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INTERNATIONAL
CONFERENCE ON HEALTH PROBLEMS
IN
TROPICAL AMERICA

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WHERE THE SCIENTIFIC MEETINGS OF THE CONFERENCE WERE HELD

PROCEEDINGS

OF THE

INTERNATIONAL

CONFERENCE ON HEALTH PROBLEMS

IN

TROPICAL AMERICA

HELD AT KINGSTON, JAMAICA, B. W. I.

JULY 22 TO AUGUST 1, 1924

BY INVITATION OF THE MEDICAL DEPARTMENT

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FOREWORD

This volume is a record of the proceedings of the International Conference on Health Problems in Tropical America, which met at Kingston, Jamaica, July 21st to August 1st, 1924, under the auspices of the Medical Department of the United Fruit Company. The object of this preface is to place in the archives the story of the Conference; also, to record the grateful appreciation of its members for the privilege of enjoying its unusual opportunities; and especially to give due tribute to Dr. William E. Deeks, General Manager of the Medical Department of the United Fruit Company, who conceived and carried out the enterprise with such satisfaction to all who took part in it.

The International Conference on Health Problems in Tropical America had its inception in June of 1923, when Dr. Deeks initiated a plan for a round table conference of the nine medical superintendents of the hospitals of the United Fruit Company in Central America. The purpose of the round table conference was to consider sanitary and administrative questions, to discuss tropical diseases, to standardize practice and to promote preventive medicine and hygiene in tropical lands. As the plan developed it became evident to Dr. Deeks that it would be advantageous to invite a few scientists who had made notable contributions in this particular field to meet with his group of hospital superintendents. The idea gradually grew until it developed into an international gathering to which eminent and active workers representing all phases of the medical and sanitary sciences connected with tropical medicine came from the four quarters of the globe. Delegates were invited to represent universities, medical societies, health organizations and governments.

Tela, Honduras, was first selected as the most advantageous place for the meeting on account of the superior laboratory facilities connected with the hospital of the Tela Railroad Company, a subsidiary of the United Fruit Company. However, as the quarters at Tela were not adequate, it was decided to hold the conference in the Myrtle Bank

Hotel, Kingston, where ample space was available both for the meetings and accommodation of the guests.

The Conference was made possible through the vision and imagination of the officials of the United Fruit Company whose generous hospitality in the way of transportation, hotel accommodations and entertainment added to the success and pleasure of the gathering. The United Fruit Company has been a pioneer and leader among corporations in looking after the health of their employes. It called the Conference with the expectation that not only would it be of value to them, but would also prove a contribution to tropical medicine the world over. In England it has long been the custom for the guilds and large business corporations to act as patrons of science and to finance the promotion of fundamental knowledge on which the welfare and progress of mankind is based. The delegates to this Conference now record with satisfaction that an American corporation has taken the initiative in an unusual and promising direction.

Following the scientific sessions at Kingston, the members of the Conference were given an opportunity to inspect and study the medical and sanitary work of the United Fruit Company in its divisions in Honduras, Guatemala, Costa Rica, Panama and Colombia. The members of the Conference take this means of thanking the government officials, medical faculties, scientific societies, corporations and private individuals in those countries, and also in Cuba, Jamaica, and the Canal Zone, for the many courtesies and facilities which they enjoyed.

We request that this statement be published as a foreword to the transactions.

For the Conference,

M. J. Rosenau

Department of Preventive Medicine and Hygiene
Harvard Medical School
Boston, Massachusetts
October 15, 1924.

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Second Row: Dr. J. G. Thomson, Dr. J. W. W. Stephens, Dr. H. R. Muller, Dr. E. Urueta, Dr. F. Fülleborn, Dr. W. E. Deeks, Dr. H. R. Carter, Sir James Kingston Fowler, Dr. M. G. Zuniga, Dr. Jose Azurdia, Dr. Geo. H. Simmons.

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Back Row: Dr. E. B. Ross, Dr. B. M. Phelps, Dr. R. B. Nutter, Dr. I. W. McLean, Dr. H. C. Clark.

ADDRESS OF WELCOME

W. E. Deeks, M.D.

On behalf of the Medical Department of the United Fruit Company, I bid you a cordial welcome, and also desire to express to you our appreciation of the interest you have shown in the Conference by your presence and your scientific contributions.

The Western Hemisphere offers a good illustration of the influence of tropical diseases in the retardation of the development of a country. A nation's progress may be gauged by the state of its agriculture, industries, and educational systems, its transportation facilities, monetary system, commercial expansion, general prosperity, wealth, and governmental stability. Judged by these standards, countries situated in temperate zones have reached a higher state of development than those located in tropical areas. Furthermore, a casual survey of a geographical map shows that favored countries in the vanguard of development have their immense centers of population mainly in low altitudes—near the seacoasts and other natural highways of transportation. On the other hand, the main centers of population in the American Tropics are located in high altitudes, the coastal plains, for the most part, being covered with impenetrable jungles.

European attempts at colonization began simultaneously in tropical and temperate zones, but the colonist in the former fought a losing battle against tropical diseases. In consequence, his progress was exceedingly slow and only in the higher altitudes was he able to gain a satisfactory foothold. On the basis of our present knowledge of tropical diseases, their etiology and transmission, it is difficult to conceive how it would have been possible for the early European incursions, to districts now infected with malaria, to have been attended with so little loss of life if tropical diseases, particularly malaria and yellow fever, had been present during the period of the Spanish Conquest to the same extent as when

the French attempted to build the Panama Canal. It is quite probable that these two diseases are not indigenous to the American Tropics, but were imported from Africa or Southern Europe.

In the low-lying American Tropics the soil is fertile, the climate equable and the rainfall abundant; in fact, everything is favorable for productivity and requires only a vigorous, healthy population to give an abundant return for the labor expended. But in these areas the perenially warm, humid climate also favors the development of the transmitting agents of tropical diseases — undiscovered and unknown enemies, against which no man up to a recent period could fight.

It is recognized when nations are at war, that the belligerent who has blockaded the enemy's ports and thus stifled international communication and commerce with those ports has gone far toward winning his battles. In like manner, the development of tropical countries has been retarded by the prevalence of endemic diseases in their ports.

Of the diseases peculiar to tropical climates, the most important in the American Tropics — in the order mentioned — are: malaria, hookworm and dysentery, although others play minor rôles.

While the cause and method of transmission of malaria are known, the problems and cost involved in its eradication are stupendous. Nevertheless, with our present knowledge of the subject, the investment necessary for the eradication of this disease, though great, pays real dividends.

An attack of malaria does not confer immunity upon an individual. Indeed, he may become repeatedly infected, thus becoming a chronic carrier, capable of infecting others. While some forms are fatal, in most cases a partial immunity develops and exacerbations of the disease occur under a variety of influences that depress vigor and vitality.

To control malaria requires either a relentless warfare against anopheles mosquitoes, which transmit the infection, or resort to quinine prophylaxis. Sometimes a combination of the two methods is advisable. The anopheles being a wild mosquito and breeding in the swamps and jungles, a warfare against them requires extensive and expensive engineering operations, such as draining and filling of the land. The

advantage of destroying the breeding places of the anopheles is that it strikes at the root of the problem. The improvement is permanent. On the other hand, quinine prophylaxis while useful is tentative. It is probable that a more effective agent than the salts of quinine now in use will be necessary to get the best results from this method of control.

It has been demonstrated that a man can not only live and be comfortable, but can continue healthy and efficient in a malarial district, provided he properly applies our present knowledge. Community control of malaria in the tropics calls for general education, legislation and individual compliance with reasonable regulations — all a part of a comprehensive campaign under skilled direction.

We are making progress along these lines as evidenced by the increasing acreage, hitherto uninhabitable, brought under cultivation through the energy and foresight of corporations that have appreciated and taken advantage of the knowledge furnished by students of tropical diseases.

In hookworm-disease there is progressive anemia, and frequently interference with mental and physical development, and sometimes premature death. In both this disease and malaria there is a loss of physical and mental vigor, and impairment of economic efficiency.

The fight against hookworm-disease is being successfully waged, and hundreds of thousands of lives are being salvaged and rehabilitated, but the problems of its eradication are enormous because of the large areas involved, the ready means of infestation, and the large percentage of population affected, particularly among the illiterate. It is, however, no longer to be considered an insurmountable obstacle to progress, and its eventual eradication is certainly possible.

In the lowlands of American tropical countries, from 40 to 100% of the native population suffers from malaria or hookworm, or both, so that there is an enormous rate of morbidity and considerable mortality, as well as a lowering of the resistance of the individuals to other infections.

The cause, method of transmission, and cure of amebic dysentery are fairly well established. The mortality caused by it has been materially reduced. In Ancon Hospital, during 1906–1908, of 170 admissions, 51 died. On the United Fruit Company plantations in 1923, of 420 admis-

sions to the hospitals, only 7 died, thanks to the use of emetine introduced by Sir Leonard Rogers in 1912, supplemented by the administration of bismuth subnitrate. The thousands of men invalided home from the Philippines during the American occupation, and from the European and Asiatic Tropics during the World War, attest to the importance of amebic dysentery as a deterrent to development and progress.

Up to a few decades ago the cause and method of transmission of these diseases were unknown; this information is necessary before any infectious disease can be prevented. Thanks to the brilliant work of that brave group of scientific men of whom you are distinguished representatives, the searchlight of investigation has gradually illuminated these fields where all was dark, and the cause and methods of transmission of most of the tropical diseases are now known. In consequence we are now in a position to act effectively in our preventive and curative measures. It was through an application of this knowledge that Cuba was sanitated; the building of the Panama Canal became an accomplished fact; and immense areas of land in tropical countries were reclaimed from primitive jungles and placed under cultivation to furnish additional food supplies to the world.

The conquest of yellow fever, which, up to three decades ago, played such deadly havoc throughout the American tropics, has been one of the brilliant triumphs of preventive medicine.

As a result of the work of the sanitary officers of Latin-American countries and the loyal assistance of their governments and of commercial organizations, directed and supported by the International Health Board of the Rockefeller Foundation, yellow fever is practically eradicated from this hemisphere, and we have every reason to believe that it will soon be as extinct as the dodo.

With the principal exception of Sleeping Sickness (*trypanosomiasis*) in Africa, the most important tropical diseases that retard development are the same throughout the world. Assembled at this Conference are representatives from the vast majority of all the important tropical areas. Your individual experiences have been varied and widespread, and you have reached more or less definite conclusions as to

the best manner of handling tropical health problems. We want this Conference to be the melting-pot of your experiences and conclusions, for the guidance of workers in health problems, not in America only, but throughout the world.

It is our belief that, when tropical diseases have been brought under control, the tide of immigration will be largely diverted to tropical climates, where the struggle for existence is accompanied by much less physical effort than in the cold and rigorous climates of the north; and that enormous areas will be reclaimed for cultivation to add to the food supplies of the ever-increasing population of the world.

We are accustomed to render homage and sing peans to, as well as heap emoluments upon, the leaders of armies whose aim is conquest and in whose wake follow destruction and death, but the leaders of the silent host of workers "engaged in the peaceful strife of science," who have braved greater personal dangers, conquered vaster territories, salvaged innumerable lives and devoted themselves to constructive instead of destructive work for mankind, have all too often accomplished their aims unhonored and unrequited.

TROPICAL HYGIENE, AN INTERNATIONAL ADVENTURE

GEORGE E. VINCENT, PH.D.

Astronomers were the first to picture our planet as a unit. To the hymn-writer the earth, in the sight of deity, became "this terrestrial ball." In the presence of a common danger each country or region sees itself a part of a larger whole. When Malthus in 1798 sounded his note of warning he had in mind the population and food supply not of one country or continent but of the entire world. With such data as he could find he attempted to forecast the future, first of each separate people, and then of the population of the globe.

It is significant that the famous English philosopher included the Tropics in his purview. He devoted special chapters to the islands of the South Sea, to parts of Africa, India, and China. His preoccupation with the various checks to population is obvious and natural. While various diseases are included in the list of checks, other factors such as famine, war, infanticide, vice are given greater weight. Malthus also disputed vigorously the idea, even then current, that tropical food supplies are automatically abundant.

The fact that Malthus did not foresee changes which for a time quite upset his calculations, does not detract from his deserved reputation for sound reasoning and an essentially scientific attitude. It is easy now to see that the opening up of new sources of food, the application of machinery or cheap labor to agriculture, the development of transportation and commerce, in short, the economic integration of the world, have not only postponed the pressure of population on food supply but have made the latter a terrestrial rather than a local issue. Swift notification of need, quick human sympathy, rapid transportation, organization for distributing supplies, minimize the effects of large-scale, acute famine almost anywhere in the modern world.

Such dramatic mobilizing of surplus food should not however blind us to the probability that Malthus' Principle

of Population is substantially true, and to be reckoned with at least by the few who may possibly delude themselves in thinking that they can forecast the future of mankind and formulate policies for its guidance. It is not cynical to assert that benevolence and charity are in themselves luxuries which only those who have a margin over bare subsistence can afford. Individuals may in crises rise to high levels of self-sacrifice for family, friends, or country, but large groups and nations are practically incapable of such conduct. Self-preservation is a racial instinct that will not be denied. If this be true, the success of Red Cross appeals for famine relief will continue to depend upon the existence of surplus food somewhere in the world.

If students of the population problem are to be believed, an indefinitely continued margin is not to be counted upon. We are told that the Malthusian law is closing in upon mankind. The recent world war is in some quarters interpreted as a warning. The breeding of banana flies in bottles is recorded in asymptote curves which by analogy are said to be the handwriting on the wall for a recklessly prolific human race. The industrializing of great populations which must import food, and the decreasing export of grain and meat from certain other regions, are declared to be premonitions of slowly but relentlessly approaching danger, grim notice that in the world considered as a whole, populations are increasing faster than the means of subsistence.

There is no denying that the people of the earth refuse to be alarmed or excited about the stealthy and imperceptible approach of a far-distant menace. The idea lacks actuality in a world full of immediate and insistent issues. The population problem leaves the average man as unmoved as when he learns that in so many thousands or millions of years the earth will freeze and all life disappear. He is more interested in the prediction that the supply of gasoline will be exhausted in the early future. Moreover, he is sure that something will turn up. Mankind is always a kind of collective Macawber. Why lose sleep over this population bugaboo? Malthus was wrong once. Why not again? Think of how much land there is? And then consider the wonders wrought by modern science.

It must be confessed that the man in the street has been

given ground for his incredulity and hope. He reads about the marvels of chemical discovery. May not synthetic foods be gathered from the air and supplied cheaply in convenient capsules? Again he hears of the vast subarctic regions in which, it is asserted, countless herds of reindeer and musk-oxen could be raised, or is told that in artificially protected waters fish might multiply almost indefinitely. And then the Tropics, especially the wet Tropics! Are not almost inexhaustible supplies of food to be drawn from these hot-houses of the earth? Surely the application of Malthus' Law can be postponed so indefinitely as to make the discussion quite academic,— or at least until something a little more rational can be done about the birth rate.

So at last we come to the Tropics in their setting as a world problem, as one possible source of at least temporary relief from the pressure of population, as a challenge to science, as an opportunity for high and fine adventure, for team-play among the nations, for generous rivalry to promote a common cause which at once includes and transcends the permanent interests of any one region or people. Another aspect of the Tropics — namely as a source of diseases which endanger other parts of the world — will be noticed presently.

There is no need to discuss at length the different theories about the future of the Tropics. A brief summary of these familiar forecasts will suffice. It is easy to understand the optimism of Gorgas. It was natural for him to think of other tropical areas in terms of Panama. Once the tropical fevers, especially malaria, are eliminated there is no reason, he said, why the white man should not remain as vigorous and strong in hot areas as in the temperate zone. He predicted a drift of white races toward the Tropics in the coming centuries. Howson, Holmes, and Mapleston, medical and health officers in the Northern Territory of Australia have given support to this idea. They declare that white men working in the open air and refusing to pamper themselves are capable of as good a day's work in the Tropics as anywhere else. The experience of the "forgotten colony of Kissa" in the East Indian Archipelago has a bearing upon this point. Eight Dutch sailors and their wives marooned on a small island in 1665 have in isolation perpetuated them-

selves, it is asserted, with little loss of energy or decline in fertility.

An almost diametrically opposite view is vigorously maintained. The tropical sunlight, either direct or diffused, is said to produce in white men physiological effects which forbid energetic and long-continued life in hot regions. Huntington sees not only the handicaps of disease and the difficulties in tilling tropical soil, but insists that contact with natives of inferior mentality is demoralizing to the white race. He believes that conditions in the Tropics tend to weaken the will of the man from the temperate zone and too generally to make him the victim of indolence, irascibility, drunkenness, and vice. He suggests, however, the rather remote possibility of slow adjustment to tropical conditions through sanitation, improved tillage, cooling devices, and frequent immigration from low levels to high, or even a seasonal movement of populations from hot regions to cool and *vice versa*.

Another theory looks forward, not to a permanent occupation of the Tropics by white races, but to an improvement in the health and efficiency of native populations under the leadership and direction of a white personnel. The vigor of this directive group will be maintained by hygienic and other measures and by return at intervals to a temperate climate. This policy is sometimes stigmatized as imperialism. The phrase, "the white man's burden," has perhaps grown a trifle threadbare. But the fact remains that as an immediate means of hygienic improvement, industrial training, and economic development, this program is in many instances being carried out with a large measure of success. It is essentially the theory upon which the Corporation whose guests we are is operating.

Still another possibility has been suggested. This is that native races in hot countries will eventually be capable of self-government, will protect health, encourage education, exploit natural resources, organize industry and commerce, and take their places as independent and coördinate units in a world system of reciprocal service and coöperation. The United States has been proceeding upon this theory in the Philippine Islands. Egypt is gaining an opportunity to test her own powers. India is looking forward to an even

larger measure of independence. The Chinese have shown capacity for commerce and are now venturing into industry. The Japanese can hardly be called a tropical people, perhaps, but their success is not wholly beside the point. If one turns to Central and South America the problem is complicated by the fact that leadership rests, not with native Indian or immigrant African races, but with a predominantly European stock. While for a long time this theory of the autonomous control of the Tropics by colored races will be held more confidently by persons who have not lived in these regions, it ought not to be ignored in a speculative forecast of a remote future.

However divergent these guesses about the future, upon one thing they agree. Whether the white race in the coming centuries occupies the Tropics, or whether these lands finally fall completely under an unprogressive native control, or whether white leadership successfully organizes colored populations, or whether these in time prove able to take over the task themselves,— in any event, protection against disease will be a fundamental necessity. Even a tropical belt abandoned to a negligent native regime would be so great a menace to mankind that concerted health measures would be inevitable. So, fortunately in spite of conflicting speculations about other things, tropical medicine has a clear call, a challenging opportunity and an inspiring goal. It must organize internationally to protect and serve all lands and people, of every zone and every race.

In this stirring adventure a good beginning has been made. The success of the enterprise depends upon: a steadily growing body of scientific knowledge, the recruiting and training of a competent personnel, efficient practical measures of control in the field, the coördination of these on a regional or even world-wide basis, adequate funds, the backing of governmental authority, and intelligent public opinion. Out of a naturally somewhat hap-hazard and nationalistic situation there begins to emerge in vague outlines at least an international organization for coping with disease as a common enemy of all nations. In this concerted campaign tropical medicine takes a prominent place.

The international character of scientific research need not be labored. To the present knowledge about tropical

diseases and their control all the leading countries have contributed.

Under the inspiration of this work of the past, research and training are going forward today in many parts of the world. There are special schools of tropical medicine in London, Liverpool, Paris, Marseilles, Brussels, Hamburg, Lisbon, New Orleans, Calcutta, Bombay, Manila. There are numerous institutes in which some tropical investigation is being carried on,— for example, the Pasteur Institute of Paris and its many branches established in various parts of France and the French colonies. The Koch Institute for Infectious Diseases, in Berlin, institutes in Amsterdam and Leyden, the Lister Institute and the Welcome Bureau in London, the Kitisato Institute of Tokyo, the laboratories of the School of Hygiene and Public Health of Johns Hopkins University, and of the Harvard University School of Public Health, the Oswaldo Cruz Institute in Rio de Janeiro, the Institute of Tropical Medicine and Hygiene in Porto Rico, and the recently established Gorgas Memorial Institute in Panama,— an admittedly defective list includes 50 centers in which investigation in various degrees in the field of tropical medicine is being carried on.

In a large number of the more than 450 medical schools of the world, investigative work of significance to tropical hygiene is being done. There are numerous serological centers, in addition to those already mentioned, in which there is undoubtedly some by-product of research. It is important not to overlook the many men and women, medical officers of health, field workers of many kinds, medical missionaries, practitioners, laboratory assistants scattered widely in tropical lands. Experience shows that from such individuals more or less isolated and without facilities or comradeship, contributions to scientific knowledge may be confidently expected. The work of the delegate from Venezuela, presented at this Conference, is a striking example of individual research.

In order that these investigators scattered throughout the world in groups or in isolated stations may work to good purpose, each must be kept informed of what the others in his field are doing. Intercommunication is maintained by printed journals and proceedings, by regional

congresses, and by migration of personnel. Forty publications dealing specifically with the diseases of the Tropics have been included in what is probably a seriously incomplete list. Of these 40, 7 are published in Great Britain, 5 in France, 4 in Germany, 3 in Italy, 2 in Portugal, 2 in Russia, 2 in Brazil, 2 in the United States, 3 in India, 2 in Africa, 4 in the East Indian Archipelago, and 1 each in Holland, Japan, and Australia. To these journals and proceedings should be added a number of medical journals, published in the Tropics, and including a good many contributions which bear directly upon the subject of tropical hygiene. There is, moreover, a considerable interchange of reprints between the various centers of investigation.

Such conferences as that of the Far Eastern Association of Tropical Medicine, which held its fifth meeting in Singapore in 1923, the First International Congress of Tropical Medicine, which met in the same year in Portuguese West Africa, and the Pan American Sanitary Conferences, which are held in various cities of Central and South America, represent gatherings which not only diffuse scientific knowledge but deepen a sense of professional solidarity and comradeship. The constant travel of colonial health administrators and representatives of public and private health agencies of many kinds also proves a stimulating influence in strengthening the bonds between scientific workers and in creating a feeling of a common task which circles the world.

The function of training personnel for service in research and administration not only is carried on through the formal schools which offer courses to colonial health officers and others who are entering medical service in the Tropics, but is a necessary by-product of the work of the institutes, laboratories, and field administration throughout the tropical areas. An increasingly important part of this educational work concerns itself with the preparation of native functionaries of various types. This work is being emphasized in India, the Philippines, the Dutch East Indies, the Straits Settlements, and in several other places. Some sort of apprenticeship system is adopted wherever hygiene measures are being carried out.

Research and the training of personnel are the conditions

of effective application of knowledge in the field. The organization of practical measures has naturally had its beginning in the colonial administrations of the various countries which are responsible for the tropical areas. Thus the British Government has through the Colonial Office established a system which extends to all the tropical possessions of the Empire. The French Government has built up a similar organization for its possessions. The Netherlands and Belgium are concerned in the same way with the health problems of the Dutch East Indies and the Congo, respectively.

Local health administrations in almost all the tropical countries have been set up in connection with these colonial services. In the Philippine Islands, the United States helped to create a health service and to give it increasing responsibility and independence. In this way a good beginning has been made in establishing under administrations for the most part centralized in Europe, widely ramifying systems of quarantine regulations and control measures within the areas concerned.

A gradual movement toward the closer coördination of these different services into something like a world-wide teamplay is significant. The first international conferences in Paris, in 1851 and 1852, marked the definite beginning of an international attempt to coöperate in quarantine methods and the control of disease. Various congresses followed, until the establishment of the Office d'Hygiene, in Paris, provided a continuing service for the gathering and distribution of information about health conditions on an international scale. The establishment of the Health Section of the League of Nations, however, is the most notable step which has been taken toward a truly international organization of public hygiene. While the Health Section includes health interest in all parts of the world, its program embraces measures of first importance for the campaign against tropical diseases.

The brilliant success of the stand which was made under the auspices of the League against the invasion of Central and Western Europe by the Plague, set a new standard of international coöperation in the control of disease. Now more than 50 nations have officially agreed to work together

in close coöperation to protect and improve the health of all peoples. As a part of this undertaking it is now proposed, under the auspices of the Health Section of the League, to establish in Singapore a center which shall serve regions of the Far East by centralizing information quickly, and by promptly notifying all concerned when conditions arise anywhere which may threaten the common safety. With the Pan-American Sanitary Bureau in Washington seeking to perform a similar service for the United States, and Central and South America, a good beginning has been made in international organization which will cover practically all of the tropical countries. Of course, it will take many years to fill in the outline which has been sketched and to organize a network of centers, personnel, rapid communication, and prompt measures of control.

In addition to official government agencies, there are commercial and privately-endowed health organizations which are playing significant parts in the organization of the campaign against tropical maladies. The United Fruit Company, under whose auspices this Congress is being held, offers a notable example of efficient medical service as a part of commercial enterprise in tropical regions. Not only have hospitals been established, but preventive measures on plantations, protection of working personnel, sanitation of steamships, and health supervision of their crews, have all been brought into an effective system which offers a gratifying measure of protection to human life and happiness, and proves that under tropical conditions economic efficiency can be secured by the proper application of modern hygiene. The planters' associations in Ceylon and similar organizations in Java are other illustrations of what intelligent business enterprise can accomplish when it recognizes preventive medicine as an essential part of good industrial administration. There is every reason to believe that with governmental coöperation large corporations operating in the tropical regions will increasingly adopt hygienic measures and become a part of a comprehensive health administration for tropical areas.

The League of Red Cross Societies has adopted a peacetime policy of promoting public health activities under the auspices of its national constituent societies. Valuable aid

has been rendered in the training of both bed-side and public health nurses, in cultivating personal hygiene among the young, in disseminating information on public-health topics, etc. While this Red Cross activity has little direct bearing on tropical conditions, it plays a significant rôle in emphasizing the idea of international coöperation.

The International Health Board of the Rockefeller Foundation illustrates another type of coöperative service. The work of this Board, supported by a large private endowment, consists almost exclusively in coöperation with government authorities. It began with a campaign against hookworm in the southern states of the United States. It has gradually extended its program to include campaigns against malaria and yellow fever, contributions to schools of hygiene, coöperation in the establishment of county health-units, contributions to the Health Section of the League of Nations, the granting of fellowships to public-health students from many countries, and a variety of other ways of temporarily assisting government agencies to inaugurate new enterprises or improve existing practice. Perhaps the most notable work of the International Health Board has been its part in creating and supporting an international attack upon yellow fever. In this, all the countries concerned have coöperated heartily. The program has consisted essentially in attacking endemic centers, and thus gradually restricting the areas within which the disease is prevalent. The undertaking has been attended with a good deal of success and the outlook is encouraging. It has significance for organized tropical-hygiene, because the work shows what can be accomplished by a closely-knit, quickly-responsive organization with expert personnel and adequate resources. Thus, at the moment there exists an organization which is prepared on telegraphic notice to send sanitary leaders to any point where yellow fever may be either reported or suspected. Appropriate measures are promptly enforced and control quickly obtained.

There is temptation perhaps unduly to exult over what has already been accomplished. When one remembers the vast areas which lie in the Tropics, and the enormous difficulties to be overcome in any actual control of tropical diseases, it is not easy to discern the dawn of a hygienic mil-

lennium, but enough has been accomplished to show the possibilities of the future, to stimulate ambition, and to awaken all who are concerned in the problem to new courage and resolution. Year by year it ought to be possible to build up an increasingly resourceful international organization for stimulating research, for training personnel, for gathering information, for establishing barricades against disease, for organizing systematic attacks upon endemic centers — in short, for minimizing the dangers and difficulties which beset life in the Tropics. In carrying out steadily, if slowly, with unfaltering faith this great undertaking, the men and women who are devoting themselves to the cause of tropical medicine are performing a great service which will affect the welfare and happiness not only of the tropical regions but of the whole world and all its people.

TROPICAL MEDICINE, 1898–1924

JOHN L. TODD, M.D.

(*Read by Title*)

In commemorating its twenty-fifth year, the United Fruit Company invited us, students of tropical medicine, to take this journey so that we might see something of the Company's work and talk together of the things which interest us. For the invitation and for the opportunities which it has opened to us, we are grateful.

Twenty-five years have passed since the United Fruit Company was established. It is a coincidence that these years, 1898–1924, span a period of wide and very great increase in our knowledge of the diseases usually present in warm climates. But in the wonderful success of the Company during that period, there is no coincidence. By increased knowledge, our northern races have conquered the Tropics. The Company is successful, and its success will continue, because today the preservation of health in the Tropics among Europeans who live there, and work with bodies and minds, is a matter of forethought, of careful administration. The quarter-century now ending has witnessed, in this, a world revolution of vast importance. It influences the future of the whole world, of all mankind.

The earliest glimmerings of history record the turnings of warmth-loving men from the cold north towards the southern sun. Down through the ages, northern men have failed to establish themselves permanently in warm climates. We said we failed to do so because hot countries were "unhealthy" for us. Only now do we understand that, lacking their diseases, the "unhealthy" Tropics may be as "healthy" for us as are our own home-lands. Medicine is now more than the healing of the sick and the protection of the well. Through its control of disease, medicine has come to be a world factor of limitless power. It permits Europeans and their animals to inhabit, and prosper in, vast areas formerly closed to them. It provides defeat for diseases which once yearly maimed and killed by millions. These twenty-five

years have brought us mastery over malaria, yellow fever, trypanosomiasis, relapsing fevers, syphilis, yaws, dysentery, typhus, and so on. This is, in truth, the heroic age of tropical medicine.

One after the other, European traders of many nationalities endeavoured to found colonies in the warm countries where they trafficked. Phœnicians, Northmen, Greeks and Romans have left records of their passing occupations dotted here and there along the shores of Africa. In later years, Spain, Portugal, Holland, Denmark, Britain and France founded colonies throughout the Tropics wherever interest called. For a time, some of these settlements were successful. Some became empires and endured in comparative success for several generations. But none of them was permanent. The conquest of the Tropics is of our generation. Today, at Panama, in East Africa, in Rhodesia, in Northern Australia, and in a thousand other places throughout the Tropics, our men and women are living and working where, twenty-five years ago, death from disease would certainly have destroyed them.

But though the great discoveries which wrought this change came so recently, it would be wrong to think that nothing had been studied, nothing learned of tropical medicine before that time. Always — and it always will be so — devoted physicians accompanied their fellows and wrote descriptions of what they saw. In the Mediterranean basin, centuries ago, Greek, Roman and Arabian physicians described malaria, relapsing fever and dysentery. Spaniards and Portuguese were the first Europeans to deal with the Indies, Africa and the Americas; so their doctors wrote our earliest descriptions of the unaccustomed diseases against which they strove. To these observations were added Dutch and British records. But, though these men wrote truthfully of what they saw, and though they discovered for us quinine and ipecacuanha, they added little to knowledge concerning the causation and prevention of disease. They often guessed shrewdly, but they failed to prove. Writings of Aristotle predicate germs; de Beauperthuy insisted that mosquitoes transmit malaria; neither proved his beliefs. They failed because they lived in the days of experience, and not of experiment. They lived in days when men gave

unquestioning belief to a teacher's dictum, and neglected to prove truth for themselves. In their time, the practice of medicine held even more deference for established opinion than it does today. Empiricism was the rule, and the watchful, unceasing doubt of the modern experimentalist was then even rarer among practitioners than it is now.

Therein lies the reason why our civilization, in touch with, let us say, malaria for generations, recognized its method of transmission only in 1898. (Authority doesn't, even yet, always act on that knowledge; during the World War, how many soldiers died because they were not protected from mosquitoes! Therein, also, lie lessons for the future and for the teachers of our profession.)

It is natural that in medicine no fundamental advance — such as Pasteur's discovery of bacteria and infection, or Lister's application to surgery of Pasteur's observation — has come from the daily bustlings of the clinician. During centuries European doctors treated typhus daily; thousands died of it yearly. Yet, before the great war, neither its cause nor its method of infection was known. During the War, the importance of the disease forced intensive study of it by many well-equipped teams of laboratory workers. Today we know that a rickettsia causes typhus and that the organism is carried by lice. Through that knowledge, Western Europe and the armies there were saved from the epidemics of typhus which killed millions farther East. The truth is this; for the usual practitioner of medicine every hour is so filled by insistent demands from professional and private life that he has no energy, no leisure of mind or body, for the recognition and consideration of things unknown to him.

Too often, also, his educators have so instilled in him a satisfying sense of complete knowledge that he ignores his ignorance and accepts the shortcomings of his art as immutable destiny. It is from physicians of another calling that practically all of the recent great advances in the science of medicine have come. Typhus furnishes the latest example of this; it is through the purposeful work of laboratories that advances in the principles, and even in the proper practice, of medicine can best be made. The great discoveries which open the new world of the Tropics to us

were made by men who studied disease both at the bedside and in the laboratory.

For tropical medicine the new period, when experience gave way to experiment, may be said to have commenced in 1880, when Laveran first *saw* malaria parasites. For some years advance was slow. Laveran's assertion of a protozoan cause for malaria received little sympathy from a profession but newly-persuaded to accept a bacillus of Italian patronymic as a substitute for "malarial miasma." A little later, Smith and Kilborne proved that Texas cattle-fever was caused by a protozoan parasite, and that the organism was transmitted from infected to healthy animals by the bite of a second host, a tick. Then Manson, fortified by his discovery that mosquitoes were carriers of filaria, suggested that mosquitoes might also carry malaria. In 1898 Ross proved that this was so; Grassi confirmed and completed his work. And then the flood gates opened!

From then until now, scarcely a month has passed without a report of some new important advance in knowledge concerning the nature, cure or prevention of the diseases of warm climates. There is no branch of medicine which has not benefited by the application of these discoveries. To achieve these successes, many men of many nationalities have worked — and have worked well. The story of their work is an inspiring chapter in the record of human endeavour. The writing of it awaits an adequate historian; one of the things which he will say is this: The history of tropical medicine, from 1898 to 1924, should inspire in man a sturdy belief that concerted and organized endeavour can solve the most difficult of problems.

Something should be said of how the work was done. In doing so, the names of three pioneers are inevitably recalled. One of them, Sir Patrick Manson, is the Father of Tropical Medicine. He was a practitioner, who refused to be bound by the limitations of his knowledge. By his searchings he broke down those limits for himself and for others. Also, he determined that other young doctors, going from Great Britain to work in the Tropics, should be better trained than he had been. It was through his representation, that the British Government aided in the establishment at London and Liverpool of the first Schools of

Tropical Medicine. That of London was particularly his. At Liverpool, the School was the work of Sir Rubert Boyce, on the academic side, and of Sir Arthur Jones, its Chairman. Both of these schools received most active support from companies of merchants and shipowners whose interests touched the Tropics.

Sir Arthur Jones was fond of saying, "Money spent in our School of Tropical Medicine is an investment, and we expect dividends from it." That expectation has been realized. The active participation of business men in the foundation of these schools furnishes an example of the way in which administrators will always provide new means for training those whom they employ, should existing facilities be unsatisfactory; the incident merits consideration from all directors of education.

The inauguration of other new institutions and of new courses of study quickly followed until now there is scarcely a capital city or a first-class medical school in any part of the world without institutions and chairs devoted to the practice and study of tropical medicine. From the beginning, it has been realized that for the prevention of most tropical diseases much intelligent coöperation from the community to be protected, is essential. Most varied methods have been employed in spreading a knowledge of these diseases and, usually, with considerable success. At present, certainly the most important single agent in the popularizing of information concerning tropical diseases is the Rockefeller Foundation. The scope of its activities transcends that of even the great national and international health authorities. The benefits resulting from its work are tremendous, world-wide and of permanent value.

It is characteristic of the investigation of tropical diseases that much of the work has been done by men who were sent to study definite problems. Doubtless, these expeditions went abroad because the diseases which they were to study did not exist at home. But it has come to be recognized that this is the best method of attacking a research problem: collect a group of investigators, each with special capacities for dealing with some aspect of the problem, equip them with every facility for their work, place them in contact with their problem, and *leave them alone*. That, in effect, is

what was done. Many instances of the success of such expeditions come quickly to mind; perhaps, in the West Indies, we think first of Reed, and of those with him, whose devotion proved yellow fever to be carried by a mosquito.

That advantage comes by allowing teams of specialists to work together upon a definitely restricted problem, is repeatedly established by incidents recorded in the history of tropical medicine, during the past twenty-five years. Similarly, other points concerning the investigation of problems in pathology have been fixed. Perhaps the most important of them is that many hours of patient search, with the best preparations and optical equipment, are often necessary before a pathogenic organism can be seen; and that the tedious hours of search are well spent because an organism once seen is positive proof of its existence. That point is illustrated by one of my own mistakes.

The first man in whose blood trypanosomes were found presented symptoms in no way resembling "Sleeping Sickness." He was a European. His chronic fever suggested that many of the cases previously called chronic malaria might in reality have been cases of human trypanosomiasis. The cases next found, Africans, showed no symptoms whatever. It was already known that tsetse-fly disease was caused by another trypanosome, and that while domestic animals were invariably killed by that trypanosome, wild animals infected with it lived in apparent health. It was thought that there might be a relation between the European and the Black resembling that between the white man's animals and the native African fauna. Nevertheless, we had considered all of the diseases of unknown causation occurring in Africa and we thought it quite possible that "Sleeping Sickness" might be due to the human trypanosome. For that reason, we examined with the greatest care, both during life and by autopsy, the only case of Sleeping Sickness which we were able to obtain.

Illness and the pressure of what then seemed more important work prevented us from searching permanent specimens at that time. The exhaustive examination of centrifugalized spinal fluid and of fresh blood-preparations showed nothing. But subsequently a search of the stained preparations of blood, made after other investigators had showed that

Sleeping Sickness was due to trypanosomes, revealed the presence of the parasites. We failed to show the connection between *trypanosomiasis* and Sleeping Sickness because we neglected to exhaust every method of examination.

That anecdote illustrates the necessity for careful search. Another of my mistakes may be recounted to show that careful searchings will fail unless the preparations examined are properly made. Trypanosomes are rarely numerous in the blood of infected persons. The only certain method of diagnosing *trypanosomiasis* is to see a trypanosome. Since the parasites are found in the blood with difficulty, it was very desirable to learn whether they might be found more easily in any other part of the body. The direct method of ascertaining whether trypanosomes are present in increased numbers in tissues other than blood, would be to excise these tissues during life or to obtain samples of them by the use of hollow needles. Because of obvious difficulties in doing so, we preferred to examine preparations taken within an hour or so after death.

Now it happens that, after the death of their host, trypanosomes soon die; and that is especially true of trypanosomes in the lymphatic glands. Consequently, though we commenced autopsies within a few minutes after death, our examination of preparations taken *post mortem* failed to reveal that trypanosomes can often and easily be found in preparations of juices aspirated from a lymphatic gland when they cannot be found elsewhere. That discovery was made by investigators who employed the direct method of passing a needle into a gland and of examining material so obtained. The anecdote illustrates the importance of patient search, of proper preparations and, especially, that in studying any problem direct methods should be used:—*Look and see.*

It is scarcely too much to say that the recognition of spirochætes, amœbæ and trypanosomes as important pathogenic agents produced a new generation of microscopists; once pathologists rarely used an immersion lens and had barely heard of mechanical stage or of dark-field illumination. In the clinical laboratory, the many uses of bacteriological, cultural methods and constant dependence upon pathological histology as observed with moderate magnifica-

tion, had somewhat prevented appreciation of the value which lies in the careful observation of good preparations with high powers. That Schaudinn, *in 1905*, was the first to recognize the treponema, which today is daily sought and seen in thousands of laboratories, is quaint commentary upon contemporary pathologists. They cultivated many a "bacillus of syphilis" and failed to look at fresh syphilitic material through an oil immersion objective! That and similar experiences, for other diseases, have made the microscope and demonstration of pathogenic agents essentials in the practitioner's daily diagnosis of disease.

Today, a wise physician is satisfied only by the direct proof of the microscope. In the practice of tropical medicine indications for action are characteristically direct. The microscope demonstrates spirochætes in the blood of a febrile patient; "606" is given and the patient is cured; lice are killed and the epidemic is "scotched." The precision of diagnosis, and consequent directness of treatment and prevention possible, for, let us say, malaria, relapsing fever, and dysentery, are rare in medical practice. Men dealing with these diseases become accustomed to direct methods; they cannot fail to be dissatisfied with our little knowledge concerning many conditions commonly encountered during practice in temperate climates. They are impatient of unexplaining empiricism, and are determined in refusing to be blind to unsatisfactory practice even when hallowed by custom. Most doctors who go from the Tropics to colder countries wonder why more is not known concerning a common cold and why quinine so often figures in its treatment.

Medicine is a profession in which there is still far too much art and far too little science. For that reason alone, familiarity with diseases that are definitely diagnosed by seeing their cause, and that are cured or prevented by patent destruction or circumvention of that cause, is valuable to students. The knowledge of such things makes students, as it does practitioners, critical and impatient of professional shortcomings in other directions. That is one of the reasons why instruction in tropical diseases should be given to all students of medicine. They should also receive it because a knowledge of these diseases is necessary to an alert and

comprehensive understanding of human pathology. The tick paralysis of children, which occurs in British Columbia and the neighbouring states, would not have remained unrecognized for so long had the men who practised in those parts been familiar with the idea of insect-borne disease.

Another reason why all medical men should know something of tropical diseases is that the "time size" of the world has become so small. Now-a-days, it doesn't take long to go anywhere! A medical student of Montreal may see in the hospitals patients who, after journeys of but a few days' duration, have brought with them diseases from Tropical America, Africa and Asia. When he graduates he may easily be called upon to practise in areas where "tropical diseases" exist. And here let it be remembered that diseases often called tropical, such as malaria, dysentery, and anchylostomiasis, often reign in temperate climates. These diseases exist wherever conditions are favourable for them. Just at present, the most striking work on the prevention of them is being done in the United States.

For these reasons, then, all physicians should know something of tropical medicine. In the United States that truth is recognized and the Association of American Colleges, in establishing a curriculum for medical students, has allotted forty hours to instruction in medical zoölogy. The pathology of tropical diseases is mainly a biological study of pathogenic parasites; that is why the term "medical zoölogy," rather than "parasitology," is employed.

In considering the history of tropical medicine, it is very interesting to recall how one discovery has led to another, often with results most fortunate for our knowledge of tropical diseases and of medicine as a whole. Among the deficiency diseases, work done on beri-beri was pioneer. Most fascinating is the sequence of researches which, interconnected and interdependent as they are, led from the trypanosomiases of animals and man to the spirochæte-caused diseases, and then from atoxyl to "606." Many similarities between the African trypanosomiasis of man and syphilis suggested that the cause of syphilis might be similar to the parasite producing "Sleeping Sickness"; the pathogenicity of Schaudinn's spirochætal organism received ready acceptance.

In the same way, it was natural to surmise that atoxyl which, empirically, had been found to be strongly trypanocidal might have therapeutic value for syphilis. Ehrlich used trypanosomes in his chemotherapeutic work, among other reasons, because of their large size which makes it easy to actually watch the effect of drugs upon them. Commencing with atoxyl, Ehrlich sought for a compound as specific in its action upon trypanosomes as is quinine upon malaria. None of the many products had that effect; but the research was widened to include syphilis. At last, came the "six hundred and sixth" with its marvelous action upon the spirochæteform parasite of syphilis. That the drug should be tried in other diseases caused by organisms of similar form, was logical. And so came our command over the relapsing fevers and yaws. Truly, all knowledge is but one; and no man can foresee the fruitfulness or the sterility of any newly discovered fact.

Although ease of travel has so lessened the "time size" of the world, and in spite of journalism and moving pictures, most of our people remain astonishingly ignorant of the Tropics and of our increasing dependence upon them for fats and food stuffs of all sorts. Perhaps the ignorance is greatest, understandably so, in northern North America. There, we have much unoccupied land and an abundance of natural products. And we have had but few contacts with the rest of the world, because we are almost self-sufficient and have no excess of population. As physicians, *we* have special knowledge of the warmer parts of the world. That knowledge places a duty upon us quite apart from our professional responsibility.

We should do all that we can to bring to those about us an appreciation of what the opening up of the Tropics means to our parent races. In our history, "land-hunger" has been a perennial cause of wars. It need no longer be so, for there are in Africa, in South America, in Australia, vacant, fertile, virgin lands where a sun kindlier than ours permits agriculture to produce not one, but four, crops in each year. The migration of the rapidly multiplying peoples of the temperate zones will soon be no longer to East or West, but towards the equator. They will find there heat no greater than that of summer in their own homes. In a climate, now, "health-

ier" than that which they leave, they will receive from a generous soil a return for labour much greater than that which they gain in the lands from which they come. It will often be unnecessary for them even to change the nature of their crops. For more than a generation, White Fathers on the shore of Lake Tanganyika have grown wheat for their own maintenance; in reporting on Northern Rhodesia the experts wrote of one area, "the finest wheat land in the world."

Our profession has opened a new world to our people. Our duty is to help them to benefit by their good fortune.

THE SEASONAL PREVALENCE OF DISEASE

M. J. Rosenau, M.D.

Periodicity is one of the interesting phenomena in epidemiology, and a more searching study of the causes of the cyclic tendency of disease discloses fundamental factors of vital importance. A number of the communicable infections tend to periodic recurrence, but very few diseases recur with sufficient regularity to allow us to predict their reappearance, with any degree of certainty. Prophecy is a test of the soundness of science. Furthermore, to be able to foretell gives opportunity for preparedness and prevention.

We know that another pandemic of influenza will some day sweep the world, but we cannot tell when this plague may recur. The intervals between pandemics have been quite irregularly spaced. Brownlee, however, has pointed out that after a pandemic of influenza, recurring waves appear at intervals of 33 weeks, provided the 33rd week does not fall between June and December; if so, the recurring waves appear in multiples of 33 weeks, in other words avoiding the warmer months of the year. This sequence was largely true following the last 2 great pandemics, 1889–1890 and 1918–1919.

Measles is an example of a disease that recurs cyclically and with considerable regularity. In endemic regions, epidemic exacerbations recur every 2 or 3 years. In large cities, the interval is usually 2 years, and in smaller communities, 3 years. The explanation of this rapid tempo in the recurring beats of measles appears to depend upon the accumulation of a new crop of susceptible children.

Infantile paralysis in Massachusetts displays a sort of regularity in the tendency to an excessive prevalence about every 4th season. These epidemic recurrences are followed

by a gradual decline until the next period, as shown by the following figures:—

Year	*Number of Cases.*
1909	923
1910	845
1911	260
1912	169
1913	361
1914	151
1915	135
1916	1,926
1917	174
1918	99
1919	66
1920	696
1921	233
1922	217
1923	221

A study of these figures shows clearly the tendency of infantile paralysis to occur in periodic phases in Massachusetts. It seems curious that this same periodicity is not evident in other places, and therefore does not appear to be a general rule. The Massachusetts figures, then, may be only a coincidence, although they indicate a definite tendency which appears to be part of the natural history of the disease in this state. Despite the vagaries and uncertainties of infantile paralysis, we know that as long as the disease prevails there will be more of it in the summer time than during the cold season. We can forecast its tendency to seasonal prevalence, but we cannot tell how much of the disease will occur. In other words, while we can prophesy the nature of the curve, we cannot forecast its magnitude. The amount of infantile paralysis is capricious and depends upon variables, which will be discussed under the causes of seasonal prevalence.

A good instance of the uncertain way in which epidemic diseases recur is shown by the visitations of plague in London from 1563 to 1680. In 1563, an epidemic causing 23,000

deaths was recorded. In 1603, London was visited by a severe epidemic. The disease then became quiescent and probably endemic for 22 years. Suddenly, in 1625, there was a devastating outbreak with upwards of 35,000 deaths. Following this, there was a long period, of 40 years, during which plague smouldered with two epidemic exacerbations, one in 1636 (10,400 deaths) and the other in 1647 (270 deaths). After 1647, the disease apparently disappeared, although in all probability it remained endemic, for it is easy to understand how occasional sporadic cases might be overlooked. In 1664–65 the Black Death in London carried off 68,596 of a population then numbering about 500,000. A graphic description of this epidemic is given by Defoe in "A Journal of the Plague Year." Numerous references to the disease will be found in Pepys' Diary. Benvenuto Cellini, in his autobiography, describes his own case. Plague is one of the diseases that have stamped themselves upon art, science and literature.

It is interesting and even instructive to speculate why Bubonic plague in London became severely epidemic 5 separate times at irregular periods — 1563, 1603, 1625, 1636 and 1665. Before plague can become epidemic, there must be a large number of complex variables in conjunction. We cannot have an epidemic of plague without first having an epizoötic in rats. At the same time, the fleas must be numerous and active and the opportunities for contact and transmission between rats, fleas and man must be close, frequent and favorable. When we realize that it is well nigh impossible to cause an epizoötic among animals in their wild state,[1] we can understand that a great number of factors determine the prevalence of the infection among the rat population. Furthermore, a severe epidemic of this sort leaves immune a large proportion of both rat and human population, so that another serious outbreak must await inflammable material. In view of the large number of factors and the number of complex variables that enter into an epidemic of plague, it would indeed be passing strange if a disease of this sort had any regularity in its periodic recurrences.

Plague is one of the diseases that have profoundly affected the economic, political and social history of civilization. I

[1] The failure to cause an epizoötic among the rabbits of Australia is an illustration.

happened to be in Stratford-on-Avon on July 11, 1914. I turned back the records of the parish register 350 years, and found recorded on July 11, 1564, the death of one Olivarius Gunne, apprentice of Tomæ Gether als Degge. Then followed this laconic statement:— *Hic incipit pestis.* Up to this time, from 3 to 5 deaths were recorded in the parish register, but from July 11, 1564, the rate jumped as follows:—

July 11–31	16	deaths
August	35	"
September	83	"
October	58	"
November	27	"
December	18	"
January	5	"

In 6 months, 245 deaths is a heavy toll for the little vicarage of Stratford. Shakespeare was a baby 3 months old when the plague broke out. Judging from the names recorded, the infection swept away entire families. Fortunately not a Shakespeare is on the list. How much has mankind lost throughout the world's long history by the untimely death of genius on account of preventable infections!

Another example of irregular periodicity is shown by the story of diphtheria epidemics in Boston, New York and Chicago. In Boston, diphtheria was epidemic in 1863–64, 1880–81, 1889–90 and 1894; in Chicago, in 1860–65, 1869–70, 1876–79–81, 1886–87 and 1890. Within recent years, such epidemic outbreaks have not taken place and the disease should never again be allowed to get out of hand.

Many other instances of the periodic recurrence of disease could be cited, but the burden of this paper is to discuss that form of periodicity which expresses itself in seasonal prevalence. Many diseases recur annually with the regularity of the perennials. Some endemic diseases are as constant as the evergreens; some are as sure as the thistles, daisies and goldenrod; some prefer the spring, others the autumn; some are like exotic plants, which will not grow at all on our soil; and still others flourish only when imported.

Seasonal prevalence is one of the most characteristic and

alluring studies in epidemiology. Many correlations are disclosed between climatic factors and the seasonal fluctuations of certain infections. These correlations do not prove causation; in fact, the more seasonal prevalence of disease is studied, the more mysterious do the causes become and the more complex the difficulties. There are many underlying influences which control seasonal prevalence other than the evident factors of weather and climate. The surface of knowledge has been only scratched — rich results await the searcher in this field; all of which adds zest to the pursuit.

The relation of season to disease clings tenaciously in common speech. "Catching cold" infers the influence of low temperature, and "summer complaint" connotes the effect of high temperature; "under the weather" implies the consequences of climate; the term "influenza" signifies a mysterious influence and even supernatural effect of our environment.

Many diseases have a seasonal curve of extraordinary regularity. They return year after year with the definiteness of the crops. However, seasonal prevalence of disease may to a certain extent be violated when a communicable infection is introduced into a virgin population. Thus, measles, influenza and smallpox do not wait for cold weather when introduced into the South Sea Islands or into a concentration camp recruited from country districts. Susceptible material of this kind may catch fire and burn freely out of season. On the other hand, when certain of the contact diseases that prevail especially in the winter time are introduced into the Tropics, they have a tendency to die out. Scarlet fever has never gained a foothold in tropical countries, and measles and diphtheria do not become serious problems under a vertical sun. Contrariwise, common colds, influenza, pneumonia and tuberculosis play havoc in warm and tropical lands, just as they do in temperate zones.

One must be unusually conservative in drawing conclusions concerning the incidence of disease in tropical countries, for morbidity and mortality records are imperfect enough at best in favored climes; they are particularly incomplete under tropical conditions. We are therefore thrown back upon personal experience and impressions:

the former is limited, and the latter may be misleading. I well remember some years ago that upon my first residence in a sub-tropical country, the existence of typhoid was dogmatically denied, for malaria was then the dominant diagnosis. We now know that typhoid fever is favored by warm weather and that this disease has long prevailed as a serious problem in tropical and sub-tropical lands.

As a rule, most diseases that have a seasonal prevalence show that this is more than a fortuitous tendency, indeed is a distinct part of the natural history of the disease. The peak of the curve of many seasonal diseases follows the latitude. Just as blossoms come out 2 or 3 weeks later in Boston than in Baltimore, so also the seasonal diseases are often several weeks later in Boston than in Baltimore. The effect of latitude is striking and significant. In the Southern Hemisphere, the season for plant life and the season for disease prevalence are alike reversed. Sometimes it is not so much the month of the year as the condition of the weather at the time which influences disease prevalence. Thus, rheumatic fever reaches its peak in March and April in the United States, but in September and October in England: both these seasons are the damp changeable times of the year.

Among the various uses of a study of seasonal prevalence is the light it throws upon the mode of transmission and other factors concerning disease, especially a disease about which our knowledge is unsatisfactory. Take infantile paralysis as an example. The prevailing tendency among public health administrators is to regard this disease as a contact infection spread by means of the discharges from the mouth and nose. Abortive and missed cases and also carriers are believed to play an important part in its spread. Infantile paralysis has a very distinct summer prevalence. Cold weather outbreaks are comparatively rare occurrences, and in this country represent almost invariably the tailings of a previous summer epidemic. The disease normally reaches its peak in August and September and usually declines sharply with the coming of cool weather. Furthermore, infantile paralysis has a predilection for rural distribution and other epidemiological factors which run counter to the epidemiology of diseases spread by contact.

A closer study of the seasonal prevalence of infantile paralysis shows that while the disease recurs with great regularity every summer, the curve is not a simple curve. A study of the seasonal prevalence of this disease by Dr. W. L. Aycock and Dr. Paul Eaton[1] in my laboratory has disclosed the fact that preceding the summer peak, there is a minor rise which takes place in the spring. In other words, there is an increase in the number of cases about March, and a subsidence in April and May before the definite rise which occurs in June up through July and August, to decline with the cool weather of September. Thus, the seasonal curve of infantile paralysis is bi-modal. The significance of this is not clearly evident, but indicates that the disease is spread in more than one way; one factor being operative to cause the minor spring rise and another factor being responsible for the summer peak. A similar study of the curve of typhoid fever shows it also to be bi-modal, thus lending countenance to the hypothesis that infantile paralysis may have several methods of spread.

Epidemics of pneumonic plague are restricted to northern climates and occur especially in cold weather. The Manchurian epidemic of 1910 occurred during the winter and was one of the most virulent epidemics of modern times, the case fatality rate being over 90 per cent. A limited outbreak, due to an infected squirrel, occurred in California in 1919. Bubonic plague occurs in the summertime and has an entirely different epidemiology. So far as seasonal prevalence is concerned, the pneumonic form of the disease follows the general rule of respiratory and contact infections, while the bubonic type runs true to form of the insect-borne diseases.

A number of diseases show two peaks, one in the spring and the other in the autumn. This is frequently the case, not only with the acute respiratory and throat infections, but also with tuberculosis, nephritis and rheumatism, as well as neuroses, which may have a higher peak in the autumn than in the spring. The causes of bi-seasonal prevalence are not at all clear.

Seasonal prevalence is wrapped up with geographic distribution and is one of the underlying factors in the distribution of disease over the earth's surface, for the reason that

[1] *American Journal of Hygiene*, in press.

seasonal prevalence naturally becomes a function of latitude. In general, diseases of the respiratory tract flourish in the colder regions, whereas in the warmer areas intestinal infections and parasitic fevers are apt to prevail.

Huntington's book on "Civilization and Climate" reawakened stimulating and suggestive studies upon the way in which climate controls human progress through its direct influence on health. Civilization has shown its greatest advance in the temperate zone. In a second publication, "World Power and Evolution," Huntington analyzes the effect of temperature and humidity on the death rate, by means of climographs. He states that the climate which is ideal for the stimulation of human progress is one in which the mean temperature does not fall below a mental optimum of 38° F. or rise above the physical optimum of 60-65° F. This ideal climate must have variability, from say 19° F. in the coldest month of the winter to 73° F. in the warmest month of the year. A uniform climate becomes monotonous; variability is stimulating and important. Huntington employs cyclonic storms as an index of variability, assuming 20 such storm centers a year as an optimum. Relative humidity is also important, the extremes of humidity and dryness being unfavorable. Within these limits moisture seems more favorable than dryness.

We know that the physical condition of the air about us has a greater influence upon our well-being than its chemical composition. A warm, still, humid day is enervating and causes a rise in our bodily temperature; this also is responsible for discomfort experienced in a close, crowded and poorly ventilated room. In addition to the physical condition of the air, there are other factors that make up the sum total of weather and climate, so far as their effect on man is concerned. We are just learning the importance of sunshine, and finding out that it is especially the powerful rays of short wave-length that influence health. That we are responsive to our environment is clear. There are seasonal changes in physiologic activity. Mental, physical and emotional status varies with the weather and in part perhaps is influenced by it. The causes of seasonal changes in health and disease are varied, complex and largely undetermined.

GROUPING OF DISEASES IN ACCORDANCE WITH SEASONAL PREVALENCE

The communicable diseases divide themselves naturally into 3 groups so far as their seasonal prevalence is concerned: (1) the insect-borne diseases, (2) the intestinal infections, and (3) the diseases of the respiratory tract.

The Insect-Borne Diseases

The group of diseases which are insect-borne prevail almost entirely during the summer time; that is, during the hot, moist season of the year, which is also the season of maximal activity in the biology of the insect vector. The insect-borne diseases give us the best examples we have in epidemiology of endemicity, and also the clearest cut instances of seasonal prevalence. We have no record of an epidemic of yellow fever in the winter time. It is not conceivable that yellow fever could prevail in any district in the absence of Stegomyia calopus. Strange to say, we have a few curious exceptions to prove the rule. Thus, typhus fever prevails in the winter season and subsides with warm weather. This paradox is explained by the fact that lice are more common in cold weather and temperate climes than in warm weather and the Tropics. The influence of temperature is well shown by the fact that typhus fever prevails in Mexico City but is absent in Vera Cruz. There is evidently something in the bionomics of the louse, and perhaps in the cycle of the rickettsia bodies, that makes cold weather favorable and warm weather unfavorable for the completion of the circle of events necessary to complete the chain from man to louse and back to man.

Even winged insects, which ordinarily are most abundant in warm weather and have their maximal flight in the summertime, sometimes cause winter outbreaks. This, however, can happen only when artificial conditions are provided. Thus, Mackenzie[1] reported an outbreak of malaria in southeastern Russia during the winter of 1922–23. The disease affected up to 90% of the population in many areas. The epidemic spread steadily throughout the winter, with the thermometer varying from 20° to 30° C. below zero from November until March. The spread of the disease

[1] *Lancet*, 1923, 55, 1225.

during the extreme cold appeared to be due to the fact that the drinking-water butt, combined with the almost tropical heat of the log houses of the peasants, afforded ideal breeding places for anopheles remaining in the huts from the summer. During the intense cold of winter, both the larvæ in the water butts and adult anopheles in dark corners could readily be found in a large proportion of the peasants' houses.

The Intestinal Diseases

The seasonal prevalence of the intestinal diseases has a general resemblance to that of the insect-borne infections. Both normally have a warm-weather prevalence. This is the case with typhoid fever, cholera, dysentery and the summer complaints of infants. The incidence and intensity of gastro-intestinal infections become greater as we approach the Tropics.

While the curve of the intestinal infections shows a marked similarity to that of the insect-borne group of diseases, the one may be distinguished from the other by the fact that winter-borne outbreaks of insect-borne diseases are unusual, whereas winter-borne outbreaks of intestinal infections frequently occur. Thus, "normal" or residual typhoid fever shows a marked summer prevalence and recurs in endemic centers summer after summer like an annual crop — provided there is a clean water supply. On the other hand, water-borne typhoid fever has a predilection for the winter season, when the water is cold. The vast majority of water-borne outbreaks of typhoid fever that have been recorded have occurred in the late fall, deep winter or early spring — avoiding the warm months. It is quite possible to tell from a glance at the seasonal curve of typhoid fever extending over a period of years, whether water-borne infection is playing a serious rôle. When cities like Albany, Philadelphia and Chicago improved their water supplies, the typhoid curve was changed in two particulars: the rate was markedly lower and the curve of seasonal prevalence was reversed.

The year before last I encountered in Russia an interesting example of seasonal prevalence. Typhus fever was epidemic throughout the winter, declining in the spring and

practically disappearing with the coming of warm weather. As typhus fever left, cholera appeared and increased during the summer, in turn to make place for typhus when the cool days of autumn arrived. The interesting part about this cholera outbreak was that so far as my investigations disclosed, it was quite independent of water-borne infection; at least, no drinking-water supply was infected on anything like the scale of the Hamburg epidemic in 1892. The summer cholera in Russia was a communicable infection in which water played a minor rôle, and its seasonal prevalence ran true to form. The seasonal prevalence of bacillary dysentery and the diarrheas of children is quite constant in all parts of the world, and correlates with the warm, moist, enervating time of the year.

Now that the summer group of intestinal infections has been largely controlled, the winter time has become the unhealthy season of the year — at least in temperate climes. The greater morbidity and mortality during the cold weather dominates the total death curve in a country like the United States.

The Respiratory Group

The diseases of the respiratory tract have their maximal prevalence during the cold and changeable seasons of the year. This group includes, first of all, the acute infections of the respiratory tract, such as common colds, sore throats, bronchitis, influenza and pneumonia. Next, there is a group of epidemic diseases, the viruses of which are spread by the discharges from the mouth and nose, which likewise have a preference for cold weather. This group includes diphtheria, scarlet fever, whooping cough, mumps, measles, cerebrospinal fever, smallpox, etc. While most of these infections have a predilection for the cold weather, it must not be inferred that they cannot occur in warm weather. As a matter of fact, they all smolder in sporadic fashion during the off season, which is probably the way in which they are kept alive. Furthermore, in addition to this occasional or endemic occurrence, many of these communicable infections break out in the summer time as veritable epidemics.

Thus, we have occasionally epidemic outbreaks of common colds, measles, smallpox, influenza, etc. in warm weather. The tendency is well illustrated in the periodicity of influenza. Following an epidemic, the succeeding waves recur at intervals of 33 weeks, but, if this point in the cycle is reached during the summer time, the periodic expectation is apt to be missed or slight. If we may trust the records of the epidemiology of influenza, there are accounts of 16 epidemics having occurred in the summer time. Despite these occasional and unusual occurrences, the respiratory diseases are clearly favored by the conditions accompanying cold, changeable winter weather, and are deterred by the warm summer season.

The respiratory group of diseases is the most prevalent and damaging to which flesh is heir, and while they prevail more especially in temperate, cold and variable climates, they occur also in warm latitudes and even in the Tropics. They are endemic everywhere. Epidemics are frequent, and pandemics sweep the world like a devastating plague about once a generation. As a group, the respiratory diseases are less well understood and hence less controllable than the intestinal infections.

Another point of special interest in connection with this group is that the usual mode of spread is by contact and through discharges from the mouth and nose. The respiratory diseases, however, may also be transferred in many other ways. Thus, infection may be contracted indirectly in food and drink, by hand-to-mouth infection, or by fomites, such as cups, spoons and other things that are mouthed.

Deaths from tuberculosis, cancer, diabetes and other diseases show a tendency to seasonal prevalence, despite the fact that these diseases in themselves are little influenced by season. This is due to the seasonal influence of the important complications of such chronic and debilitating affections. Thus, deaths from diabetes show a curve corresponding to that of pneumonia and bronchitis. The complications dominate the picture.

Another interesting factor in the cold-weather prevalence of common colds, influenza, bronchitis, sore throat, pneumonia, measles, scarlet fever, diphtheria and a long list of diseases spread by the discharges from the mouth and nose,

is that in all of this group contact infection is the main mode of spread. The spread of disease by contact implies close personal association. Close association favoring the spread of contact infections under poorly ventilated and crowded conditions is a concomitant of cold weather. In winter there is a tendency to huddle together; in summer, to spread out.

Crowding, then, is believed to be a factor which accentuates the tendency to the seasonal prevalence of the contact diseases. On the other hand, it cannot be the dominating factor, for we sometimes see these very same diseases occurring as sharp outbursts in the summer time, in the Tropics and even under rural conditions. Influenza spreads like wildfire in sparsely settled country districts. A contact epidemic may break out at any season and, once started, runs its course in spite of weather or climate. Epidemics of smallpox and measles occur in the summertime. Gorgas found pneumonia to an excessive degree in a warm country such as Panama. This was aggravated by overcrowding and a susceptible population.

Diphtheria shows a wide seasonal range. An outbreak may occur at any time of the year, but is much more likely to happen in the early winter than at any other time. Diphtheria is a disease of cities and of colder latitudes. It is rare in the Tropics and sub-tropics, even in large cities. In other words, the prevalence of diphtheria depends upon two factors, climate and concentration of population. The death rate in northern states and cities is generally higher than in the southern. Scarlet fever is more variable in its occurrence than diphtheria. High points may be reached at any time from the autumn to the spring; the disease is rare in summer. Measles shows wide seasonal variation. The peak of the curve usually occurs in the cold weather, but may be reached in the summer months of June, July or August.

One of the most interesting facts concerning seasonal influence on disease is the agreement to be noted in cities widely separated and of diverse climates. Much more could be learned by comparisons of this sort.

Hence, neither the condensed, crowded, *gel* state of humanity in the winter, nor the *sol* state of dispersion in

the summer, is an adequate explanation of the seasonal prevalence of the respiratory group of diseases.

A Discussion of the Causes of Seasonal Prevalence

The causes of seasonal variation in the prevalence of disease are varied and complex, and not well understood, but they are enticing fields for study. Some of the probable causes, such as the direct effects of weather and climate, the features of crowding, and the problems of susceptibility and immunity, have already been touched upon. These and others lend themselves to discussion.

There may be a lowered resistance, which expresses itself as an increased susceptibility at certain seasons of the year. On the other hand, there may be an acquired immunity of part of the population which acts as baffles against the spread of infection. There may be heightened virulence on the part of the parasite, or if not increased virulence, at least heightened activity, so that its powers of penetration, invasion and primary attack are facilitated at certain seasons and handicapped at others.

The susceptibility of the population helps us in part to explain periodicity, but throws little light upon seasonal prevalence. Thus, a severe epidemic of smallpox, plague or typhus fever will leave meager susceptible material for another outbreak. Yellow fever in an endemic area is kept alive by non-immune immigration and new births. It is the fresh susceptible material that feeds the flame. The disease will die out in a city with no influx of strangers, the new-born being insufficient to keep the fire burning. On the other hand, the 2-year periodicity of measles is accounted for by the susceptible crop of new babies. This explanation, however, does not satisfy Brownlee, who regards the well-known cyclic recurrence of this disease as due to some factor in the life history of the parasite, still unknown. It has been observed that measles shows little tendency to spread during the odd year, despite the presence of susceptible material. Susceptible population in itself is not a satisfactory explanation of the recurrence of disease at definite seasons of the year, although it is evident that seasonal prevalence depends upon susceptible material.

The amount of disease in the community depends to a certain extent upon the amount of virus as well as upon the facilities for its transfer and related influences. The amount and distribution of the active principle is probably one of the prime underlying factors in the generation of some diseases in epidemic proportions. With some crops, the amount of the harvest depends primarily upon the quantity of seed and its distribution. Studies in experimental epidemiology, by Webster, indicate the importance of this factor in epidemics of mouse typhoid. Other diseases, such as smallpox and measles, probably propogate themselves entirely independently of the amount of the virus. This is not the case, however, with streptococcic sore throat, which is believed by Bloomfield and Felty to correlate with the amount of the virus and facilities for transfer by close and prolonged contact during cold weather. Dudley has discussed this matter from a clinical standpoint and brought out the principle which he refers to as "the velocity of infection."

Dosage, or the number of bacteria, also is an important element in determining disease as well as the amount and distribution of the causal agent in the community. It takes at least 10 virulent tubercle bacilli of a certain strain to infect a guinea pig. It requires many more tubercle bacilli by the mouth than by the lungs to induce tuberculosis. On the other hand, strains of plague and pneumonia may be so virulent that one bacterium is enough to start a fatal infection. Dosage varies with different infections, and with the same infection under different circumstances.

Webster [1] reminds us that the equilibrium of an infectious disease in a given community is determined essentially by 3 factors: (1) microbic distribution (2) microbic virulence, and (3) host susceptibility. If an epidemic is to be averted or modified, one of these factors must become changed. Webster's studies on mouse typhoid plainly indicate that the inherent virulence of each strain of this bacillus remains constant. He therefore regards virulence as a relatively fixed quality. Racial immunity is acquired slowly if at all. Consequently, the control of epidemics of mouse typhoid depends on influencing microbic distribution. Streptococcal infections in man, such as hemolytic sore throat, scarlet

[1] *Am. Journ. of Hygiene*, 4. 34. 1924

fever and erysipelas, are milder and probably less frequent than formerly. It is quite likely that these infections are becoming less prevalent than formerly, and less severe because of the measures taken among hygienic people to prevent the distribution of large numbers of virulent streptococci broadcast among the people. In other words, the population now is probably much less heavily seeded with virulent streptococci than it was before the days of isolation, disinfection and understanding.

The seeding of communities with a virus is therefore an important element in epidemic and endemic prevalence. Cerebrospinal fever occurs usually in cold and changeable weather. Carriers are common in the winter time, rare in summer. The carrier state is persistent in cold weather, but recedes spontaneously on the coming of warm weather. Camps in warm climates for carriers of meningococci were advocated during the World War.

Common colds increase the number of pneumococci in the mouth. Normally, about 50% of the healthy population are carriers of pneumococci. This percentage jumps materially in persons who have common colds. Pneumococci, as well as Pfeiffer's bacillus and other mouth organisms, increase during attacks of influenza, whooping cough and measles. Scarlet fever seems to cause an increase in the number of diphtheria bacilli in the throat, and a somewhat similar symbiosis is found in the epidemiological relation between other infections.

In a well-seeded community in which an equilibrium has been reached between host and parasite, the introduction of susceptible persons will cause an epidemic occurrence not only among the newcomers but also among the old residents. This can be explained by the fact that the new and susceptible are attacked, and this increased number of new cases causes a general increase in the amount and dispersion of the infection. In other words, the equilibrium reached between the host and the parasite in endemic regions can readily be disturbed so that an epidemic outbreak results. The changes in the body due to season may likewise disturb an equilibrium sufficiently to account for the seasonal tendencies of some infections.

What effect carriers may have upon seasonal fluctuations of disease is not at all clear. The carrier state itself shows seasonal variation in several instances. The best example is found in meningococcus carriers, which are comparatively frequent in cold weather, and relatively scarce in warm weather. In diphtheria, the carrier state has been studied both as to season and as to virulence. The number of virulent carriers is directly proportionate to the number of cases, and the seasonal curves of the two therefore largely correspond. It is rare to find a virulent diphtheria bacillus in a normal throat or nose, except in persons who have had direct and recent contact with a case of the disease. Carriers explain the vagaries of endemic cases; they account for water-borne outbreaks of typhoid fever and milk-borne epidemics of scarlet fever. Carriers are the storehouse of infection between epidemics, but they do not explain the seasonal prevalence of disease.

The question of virulence and its relation to season is still an unsolved problem. Some infections, like typhoid fever have quite constant case fatality rates in all seasons, in all places, and in both endemic and epidemic situations. With typhoid fever, then, it is possible to construct a satisfactory curve of incidence from the mortality records. This is not so with most other diseases.

The relation of virulence to disease is fundamental, and the solution of the problem will require accurate data before a statement can be made with any assurance of finality. Furthermore, this question must be settled for each disease separately, for each disease is a law unto itself. A number of diseases show marked changes in severity at different times and under different circumstances. I have been through some yellow fever epidemics with a case fatality rate of 37%, and through others a few years later in which the rate was less than 5%. I have also seen still greater variation with smallpox. Scarlet fever is now much milder on the average than formerly. Records of epidemics of infantile paralysis show a great variation in virulence — from 5 to 30.7% case-fatality rate. Flexner and Amoss have shown that strains of the virus passed through monkeys under laboratory conditions fluctuate in virulence from time to time.

We do not know whether disease is more or less fatal on the up or the down curve of an epidemic. There is evidence to show that as an epidemic dies out, the disease becomes more severe, and this has been explained by the fact that as the disease is on the run, the very susceptible are chiefly attacked. Probably the best studies with complete data on this score are those of the great epidemic of infantile paralysis in New York in 1916. This was the most extensive epidemic of this disease in the history of the world — 29,000 cases and 6,000 deaths. The case-fatality rate was 27 per cent throughout the rise, peak and fall of the curve. Dr. W. L. Aycock and Dr. Paul Eaton[1] made a study of 38 different epidemics occurring in various parts of the world between 1894 and 1921, comprising 20,568 cases, in which the maximum case fatality was 30.7 per cent, the minimum 5 per cent, and the average of all 20.8 per cent.

Even in a well-organized community where public health administration has reached a high level of excellence, the reporting of deaths and especially of cases is imperfect and incomplete. There are many sources of error. There are fashions in diagnosis which have their vogue, and pass. Furthermore, there is a psychology which influences diagnosis and the reporting of disease. Thus, a newspaper scare will at once cause a jump in the number of reported cases and deaths, especially in the group of ill-defined diseases. This is notably true of influenza. Often typhoid fever and infantile paralysis rise with the intensity with which attention is directed to these diseases, and fall when they pass out of mind.

In a study made by Dr. Aycock and Dr. Eaton in my laboratory[1], it was found that in infantile paralysis, the case-fatality rate is much higher in cold weather than during the summer season. This would indicate that the disease is much more severe during its sporadic occurrence in the off season, than during its summer prevalence. A deeper study of this phenomenon, however, throws serious doubt upon this inference, for experience indicates that infantile paralysis has about the same case-fatality rate the year round. It is probable that during the off season only the occasional severe and fatal cases are recognized and reported, while a larger proportion of those of the mild and ordinary

[1] *American Journal of Hygiene*, in press

type occurring in this season are missed than during the months when the disease is conspicuously in mind.

Generalizations concerning seasonal prevalence are hazardous, for each particular infection has its own vagaries. Each disease must be studied in and out of season. Its prevalence may then be correlated with other factors in order to get a true epidemiological picture.

The parasite has its own problems and struggle for existence. If it becomes too malignant and destroys the host before it can get out, it defeats its own purpose. The adjustment towards an equilibrium is therefore complex and exceedingly intricate.

Many diseases follow the temperature curve so closely that there seems to be a direct causal relation between temperature and seasonal prevalence. When the matter is studied a little more intimately, temperature as a direct cause is not so evident. We have the testimony of Arctic explorers that there is little pneumonia among the natives and among those visiting polar regions. It seems also to be a matter of observation that when Esquimos and Laplanders come to our climate, they are especially liable to the pneumonias, and the fatality among them is great.

We have the statement of the Grenfell expedition that influenza when carried to the countries of Greenland caused havoc, with a very high mortality, among the natives. Other reports coincide with this experience. Epidemics of pneumonia and influenza are not confined to cold or even temperate zones, but are seen quite frequently in the Tropics. Pneumonia is one of the chief causes of death among the laborers on the fruit plantations in Central America. According to Vaughan, studies in Michigan show that the lower the temperature, the greater the number of cases of pneumonia in that state. The warm cities in the United States have less pneumonia than cold cities, but the warmest city does not have the lowest rate, nor does the coldest city have the highest rate. Temperature alone, therefore, is not the deciding factor.

Scarlet fever shows a distinct relation to temperature. The disease is usually high in the colder cities, and almost absent in Atlanta, Los Angeles and New Orleans; it does not even appear in the Annual Report of the Chief Health

Officer of the Panama Canal Zone. Diphtheria differs materially from scarlet fever, in that it is prevalent in warm as well as in cold regions. Measles, while showing a very distinct preference for cold weather, prevails in both cold and warm countries.

According to Huntington, the death rate increases as the temperature departs in either direction, hot or cold, from the optimum, which is around 64° F. Furthermore, whatever this death rate, moisture lowers it. At 64° F., humidity has the least influence. This is indicated for the total death rate, for deaths from non-communicable diseases and from pneumonia, as worked out by Greenberg for certain eastern cities and by Vaughan for Detroit.

Temperature is only an index of the many complex factors that make up the sum total of season and climate. Heat is depressing, cold is stimulating. The ill effects of bad air and the good effects of fresh air are due primarily to the physical condition of the air which influences our heat-regulating apparatus. We manufacture more heat than needed, and therefore we must lose heat in order to prevent heat stagnation. The loss of heat depends largely upon temperature, humidity and the motion of the air about us. When, however, we consider seasonal changes, we bring in other factors, such as sunshine, storm and variation.

Seasonal influence cannot be ruled out as Huntington states. In other words, the highest death rate in the spring may not correlate with dryness, but with the fact that people are more fatigued by the strain of winter and are as a rule less resistant to pulmonary infections. One of the causes of seasonal prevalence may be the stress of increased heat production and metabolism. The body becomes weakened as the winter season goes on, and pneumonia continues to increase until the advent of warm weather in the spring. The peak of the disease is reached at different months during the winter in the northern United States, but in any case there is always more of the disease in February than in August. In other words, temperature seems to exercise a greater influence, so far as pneumonia is concerned, than moisture.

Vaughan offers the interesting speculation that it is not

so much the cold or cold weather that affects us as our semi-civilized response to this cold. Outdoor cold drives us to live in overheated atmospheres indoors. We spend our winter days in temperatures between 70° and 80° F. Houses are overheated, factories are overheated, and offices and stores are overheated. It is this fact which helps explain the apparent contra-indications in the effect of weather on pneumonia. Physiologically, cold is stimulating and heat is depressing. Practically, cold weather places a greater strain on the body in metabolism and in waste elimination. The body is more exacting. Working under a heavier schedule, it must not be denied its rest. If given a chance — ample sleep, living in cool rooms — the body responds to the stimulation of winter.

It is said that tuberculosis patients do much better in the cold season. Sick people so care for themselves as to counteract the unfavorable concomitants of cold. By so doing, they are in a position to reap in full the benefits of cold. Arctic explorers are not prone to pneumonia. Thus, it is the habits of life which cold weather induces, rather than the weather itself, which lead to this disease. It is for this reason that we may regard much of the pneumonia as humanly preventable. Studies have shown that it increases as physical vitality decreases. When this fact is fully sensed, Vaughan believes that we will adopt the habit of easing up in February and resting in order to counteract fatigue. A more thorough knowledge of the weather combinations will place us on guard in the future, and when the relation between weather and disease is better understood, we may be able to predict the health outlook and even prepare in advance for eventualities.

It is assumed that the limitations imposed by weather and diet cause many persons to lead unhygienic lives in winter. For some of these, spring brings a welcome tonic change; others seek such a change by removing to a different locality. Taking a spring tonic may have been an old-fashioned notion, but it was moreover an expression of the influence of winter conditions.

A change of climate brings more than a change of scene, and its effects are often real. A change of climate may bring rest and recreation, and it also brings the influence of

latitude, diet, temperature, moisture and sunshine:— it not only means favorable weather conditions, but also removal from smoke, dust and other noxious influences in the air, water and food of the environment in which the person lives. Even the psychologic influences that come with such changes often account for the benefits. When it is all summed up, we must admit that the favorable effects of a change of climate may be due to causes that are not understood at present.

The value of sunshine has always been appreciated, but we have understood its importance only since the work on heliotherapy in tuberculosis, and more particularly the comparatively recent observations upon the health-giving virtues of the direct rays of the sun in preventing and curing rickets.

It is extraordinary that the utilization of certain foodstuffs depends upon sunshine. The rays of short wavelength in sunshine have great power to influence the chemical and physical processes of life. Certain substances in buckwheat, also hematoporphyrin or eosin, are not harmful if the animal under observation is kept in the dark, but exposure to sunshine causes serious and even fatal injury. The photodynamic activity of sunlight must greatly influence our well-being both in and out of season. Esquimo children escape rickets because they eat the livers of fish. The negro child in New York is apt to develop rickets unless given cod-liver oil.

It has recently been shown that even the weight of certain organs in the body varies with season and directly with the amount of sunlight. Sunlight, then, is one of the potent influences that make up the sum total of climate, and explain the seasonal variation in some diseases.

Climatology, from the human standpoint, has not yet reached the dignity of an exact science. It still banks on combinations of tradition, unverified beliefs and empiric deductions.

A natural explanation of the winter prevalence of contact infection is the condition of crowding in cold weather in contrast to the tendency to dispersion in warm weather. Diseases spread by discharges from the mouth and nose are favored by close personal association. People who live

together, eat, sleep, work and play together, furnish multiple opportunities for the transmission of infections of the class in question. During the World War we found that messmates would run as high as 60 and even 80% of carriers of meningococci. Bloomfield studied the seasonal prevalence and epidemiology of septic sore-throat among the nurses of the Johns Hopkins Hospital, and found that intimate and prolonged association was a factor in the transmission, during the winter time, of sore throat due to a hemolytic streptococcus. Gorgas found crowding to be one of the factors in the excessive prevalence of pneumonia among the miners on the Rand in South Africa. It is unnecessary to multiply instances. The effect of crowding is well known,— yet it does not give a satisfactory answer to seasonal prevalence.

The schools have also been implicated in the increased prevalence of certain diseases in the fall and winter. Students of the subject, however, are satisfied that the schools have comparatively little effect upon the seasonal curve of cold-weather infections. Vaughan states that the seasonal curve of disease implicates the weather more than the school. Lobar pneumonia certainly cannot be influenced by school attendance. In spite of the opening of school, the peak of scarlet fever is not reached until January, and a secondary high mark occurs in April. Measles is even more deliberate and fails to reach its maximum until May. Vaughan believes that there is nothing in the behavior of these diseases which involves the school as a breeder of diseases, and states that it is the weather influence in the long run which controls the form of the curve.

In man, as well as in the lower animals, there are distinct seasonal changes which at first sight seem to have nothing to do with disease. The best known of these is hibernation. There is also a seasonal period for reproductive activity. Many animals show variation in the growth of hair, feathers and antlers at different seasons of the year. These and other periodic physiological activities may be underlying factors in the seasonal prevalence of some diseases. Seasonal changes in metabolism in the lower animals are well recognized.

Beckmann,[1] in a consideration of the effect of season on disease, attributes the absence of such marked seasonal

[1] *Deutsch med. Wchnschr.*, 1922, 48, 1409

alterations in man to the fact that with higher development comes a better regulating-mechanism against extraneous influences. But even in man there are distinct alterations in metabolic activity at different times of the year. Thus, measurements have shown that in spring the hair grows more rapidly than at other times; body activity as a whole is lessened in winter, so that the usual amount of time spent in sleep is much increased over the summer-sleep among people not too artificially regulated by customs and alarm clocks. Presumably, this is related to hibernation in other species. It is said that pulse rate, temperature and respiration are highest in winter, and recently it has been found that the height of the capacity of the blood to bind carbon dioxid is reached with the shortest days of the year. In the spring there is a distinct fall in the carbon-dioxid tension of the blood, which implies a decrease in the alkali reserve.[1] Although these variations are exceedingly small, they gain in the possibility of significance through the fact that they appear at the time of year when most diseases of seasonal variability are making themselves manifest, excluding diseases dependent on such obvious seasonal matters as insect transmission and food supply.

Man's heat-regulating apparatus is better than that of many of the lower animals. Nevertheless, it is responsive to external temperatures. Thus, a stay for 3 hours at 40.4° C. with a relative humidity of 95% will cause a rise of several degrees in the temperature of the body. Likewise, a lowering of body temperature soon results when either the whole or part of the body is exposed to cold air or immersed in cold water. The classic experiments of Pasteur with chickens, which are rendered susceptible to anthrax if their feet are kept in cold water, is pertinent in this connection.

An illuminating instance of the effect of climate upon physiological activity is found in the laborious observations made by the pioneer American physiologist, William Beaumont, on the gastric conditions in his classic patient, Alexis St. Martin. He recorded with great care the meteorological details, and from one group of experiments concluded that "the variations of the atmosphere produce effects on the temperature of the stomach, a dry atmosphere increasing and a humid one diminishing it."

[1] *Journ. Amer. Med. Asso.*, 1923, 80, 476

Seasonal prevalence is also associated with endocrine imbalance. Hibernation is known to depend upon the activity of certain ductless glands. The way this may affect disease directly and indirectly is evident. Moro found that the incidence of infantile tetany increases in January and February, rises to a peak in March, and falls nearly to zero in the summer. The galvanic irritability follows a similar curve, and in guinea pigs a seasonal variation has been found in respect to their sensitiveness to caffein. Even mental instability has a seasonal tide, for the curve of suicide shows a definite peak in the spring. Other mental disturbances follow a similar curve, with a second rise in the autumn in some types.

Hyperchlorhydria is said to show a distinct rise in the spring and autumn, which may possibly be correlated with the diet. Hyperthyroidism seems to show a double curve. Rusznyak[1] believes that the change from winter to summer or from summer to winter arouses an adaptive mechanism, the activity of which produces a condition of instability during these transition periods, and hence pathologic conditions become more conspicuous until seasonal adjustment is completed.

A very interesting contribution to this subject by Brown, Pearce and Van Allen[2] has just appeared. They studied seasonal changes in organ weights and their relation to meteorological conditions. It is well known that many of the endocrine glands of normal animals undergo rhythmic changes in weight per unit of body weight, which conform in general with seasonal conditions. The authors named found that in the case of organs such as the heart, the kidneys, and the liver, the transition from one condition to another occurred relatively slowly, and the maximum variation in any direction was distinctly less than that noted in the case of a number of the endocrine glands and the lymphoid tissues. The heart and kidneys showed a variation in weight amounting to approximately 20% while that of the liver reached upwards of 40%.

On attempting to correlate this series of seasonal variations in organ weight with meteorological conditions, it was found that the majority of them corresponded in time and direction with prevailing conditions of sunlight. In general,

[1] *Wien. Arch. f. inn. Med.*, 1922, 3, 379
[2] *Proc. Soc. Exp. Biol. & Med.*, 1924, 21, 373

the periods of maximum weights coincided with the high levels of daily sunlight, while the periods of minimum weight coincided with the low levels of daily sunlight. Furthermore, the change in direction and the transition from that condition to the other corresponded with the change in sunlight from winter to summer, or from summer to winter. What is more significant, however, is the fact that the actual time and progress of the change followed the curve of the actual hours of sunshine, rather than the theoretical curve or the uniform progression of the seasons. This was more noticeable in the case of some organs than of others. In fact, it appeared that the weight curves of some organs conformed more closely to the curve of temperature or to humidity than to the curve of sunshine, and that the degree of correlation in any case was subject to the influence of other factors. In other words, in the size and weight of organs there are actual changes which pursue a rhythmic course in harmony with the progression of the seasons.

The study of epizoötics under laboratory conditions very closely simulating natural conditions is a new angle of approach, and should throw light on the causes of seasonal prevalence. Topley in England and Flexner and his associates[1] in this country have studied mouse typhoid produced experimentally in laboratory animals. Experimental epidemiology with different types of infection carried out over long periods of time, and under controlled conditions, offers opportunity to unravel some of the mysteries of epidemic disease and its seasonal prevalence.

Hunt was the first to show the influence of diet as well as of season in the susceptibility to certain poisons. He demonstrated that mice are much more suceptible to a poison (acetonitril) in the spring, following the winter diet, than at other seasons of the year. The familiar spring outbreaks of pellagra follow the limited and one-sided diet of the winter. The eruptions of pellagra on the exposed surface of the body resemble sunburn, and may be activated by the rays of short wave-length. The seasonal prevalence of rickets in the spring is explained by the long-continued absence of sunshine during the winter time. Scurvy is naturally influenced by season, depending upon the vitamin-bearing food which

[1] *Proc. Nat. Acad. Sc.*, 1921, 7, 319; *Journ. Exp. Med.*, 1922, 36, 9

is accessory. Stall-fed cattle in the winter time secrete a milk containing little or no antiscorbutic vitamin, whereas milk from pasture-fed cows contains this important property. The seasonal character of certain cutaneous disorders is explainable on the basis of sunlight, while in others dietary variations are probably responsible. In some instances, as in teakwood poisoning, the lesions do not appear until after the activating effect of sunlight.

We see, therefore, that the seasonal prevalence of disease may have a number of different explanations. In some cases it is dominated by temperature, in others by combinations of temperature, humidity, air movements and other factors that make up the sum total of weather and climate. In some instances it is due to diet, in others to changes in susceptibility and resistance, as a result of seasonal factors. Virulence probably plays a rôle. Sunshine is an important factor in a group of maladies. Again, there is the normal seasonal fluctuation in the physiological mechanism of plants and animals, which is probably a response to the seasonal changes in our environment.

The comparison of epidemics with forest fires is a useful analogy and gives rise to such expressions as "the epidemic burned itself out," or "the epidemic smouldered," etc. These are figurative expressions, however, and do not explain the course of the communicable infections; in fact, epidemics are living things.

The epidemic diseases are phenomena obeying the laws of life, and we should expect them to have seasonal fluctuations, just as we commonly observe the influence of season in the plant kingdom. We know that temperature, moisture and sunshine are dominating factors in determining the appearance of blossoms and the activity of corn and thistles, and while each plant seasonally returns with great regularity, the amount of the crop correlates very definitely with a multiplicity of factors, such as the number of seed, the food in the ground, moisture, temperature, sunshine, etc. The amount of the crop, however, is not always determined by the co-incident factors of weather, but may be a summation effect, the results of 2, 3, 4 and even 5 preceding seasons which will determine whether we are to have a good crop or a great epidemic.

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DISCUSSION

Sir Arthur Newsholme (Opening the Discussion).—I am sure I am expressing the views of every one present in thanking Professor Rosenau for the very able and interesting presentment he has made of this fascinating subject, in spite of the fact that he has been able only to touch on some of the points. We hope to have the opportunity of reading his paper in full at a later time. The whole subject is one of great fascination and Professor Rosenau has done something to elucidate it.

I should like to ask him in regard to the variations in the seasonal prevalence of certain epidemic diseases in several states of the United States. Some months ago I was doing a little work on this problem and was struck by the fact that in typhoid fever, for instance, the maximum month of incidence in some southern states was May or June. Further north it was August and September, and there was no uniformity of seasonal incidence in the United States, in striking contrast to the state of things in Europe. It was very interesting to note that the seasonal incidence of this disease is controllable.

A similar variation of the seasonal prevalence of infant diarrhœa occurred in various parts of the States. In connection with this it is interesting to note that some of the seasonal incidence of some of these diseases, too, is controllable. For instance, in England, the rule for typhoid fever is that it begins to become prevalent in September, reaches a maximum in November, and gradually declines during the rest of the year. During the past 10 years the autumn rise in typhoid fever has almost disappeared, and I remember very well a distinguished army medical officer coming to my office during the World War and referring with perfectly justifiable pride to the fact that they had been able in the army in France almost to prevent the occurrence of typhoid fever. He was somewhat surprised when I drew his attention to a diagram on the wall of my own office which showed that in the civilian population in which there had been no inoculation against typhoid fever, and

where there had been no unusual chlorination of water, we had secured extraordinary diminution in the incidence of typhoid fever so great that the autumnal rise of the curve no longer appeared.

I am not suggesting for a moment that inoculation against typhoid had not been successful under army conditions. It had, but there were causes operating in the civilian population, — sanitation, improved water supplies, detection of contacts, etc.— which had caused the almost complete disappearance of the seasonal autumnal increase of this disease. Eventually we may arrive at the same state of things in regard to some other epidemic diseases and find that the curve of incidence will become gradually controllable.

There is another aspect of periodicity which is important. It can, as Professor Rosenau indicated, be introduced as a means of prophecy of what is likely to happen. That is so, particularly in regard to smallpox in England, where the seasonal maximum occurs in May or June. If an epidemic occurs in January the health officer is anxious; if he gets a few cases in May or June he is not anxious, because he knows that the normal seasonal period is at an end, and that he probably will have an interval of 5 or 6 months in which he can adopt further precautions.

Another important aspect of this subject is the occurrence of cycles of dry years and their influence on the curves of epidemics. Dr. Longstaff first worked at this, and he showed a definite correlation between a succession of dry years and an excessive amount of erysipelas, scarlet fever and acute rheumatism. Working on the same subject at a later period I found, after very careful inquiry into the actual annual incidence of rheumatic fever in Australia, South Africa and Europe, that rheumatic fever occurred in epidemics when there was a succession of dry years; in other words, when in a succession of years the total annual rainfall was deficient.

It is perfectly clear, as Professor Rosenau has indicated, that total rainfall is a complex factor; but it is a phenomenon of some practical importance to know that in years of excessive drought, especially when 2 or 3 of these years succeed one another, scarlet fever, rheumatic fever, and, as I have also shown, diphtheria, occur to an excessive extent. These dry cycles have an important bearing in regard to some of our chief epidemic diseases.

The subject is one which is most fascinating and interesting, and we are very greatly obliged to Professor Rosenau for the way in which he has introduced it to us.

Dr. C. A. Kofoid.— To the biologist Dr. Rosenau's discussion of the "Seasonal Prevalence of Disease" presents many striking parallels to the occurrences of organisms elsewhere in nature. The

cosmic forces which determine temperature, rainfall and the access of radiant solar energy to the living world are correlated not only with the organisms productive of disease, but in an infinite variety of ways with the life cycles and occurrences of plants and animals generally. The ecologist can measure the temperature limitations, the conditions of humidity, and the amounts of sunshine which set bounds and limits to the living world. Therefore, not only disease germs but their insect vectors and their reservoir hosts, as well as the human organism, are responsive to these forces of cosmic origin.

A 6-year study of the plant and animal population of the Illinois River, prior to the opening of the Chicago Drainage Canal, and a 16-year study of the quantity and character of the life in 3 reservoirs supplying the City of San Francisco, made by me are full of instances of these rhythmic and repeated seasonal recurrent curves of the constituent elements in those microscopic populations.

The cyclic recurrence of infantile paralysis in periods of 3 or 4 years, in the light of Dr. Brues' suggestions of a possible relationship of this disease to rats, is of interest. It might be that this periodicity is in some way correlated with the length of life of the rat — a possible carrier — and of a varying susceptible element in that population. The studies of Dr. Sewall Wright on the varying susceptibility of guinea pigs to tuberculosis have proved the existence of varying grades of susceptibility, in this rodent, which are of genetic origin and therefore heritable. It seems probable, therefore, that any epidemic dependent upon some reservoir animal, such as the rat for example, would exhibit a periodicity determined in part at least by the persistence of the more resistant elements in the reservoir stock after an epidemic, and the subsequent increase of the less resistant in the years that follow, until a new epidemic again reduces their numbers. It is evident to the biologist that genetics has a contribution to make to epidemiology.

Major George C. Dunham.— Dr. Rosenau mentioned the introduction of a factor into the situation which may modify the seasonal distribution of infection. During the World War we found that in the camps in the South, where the draftees were largely from rural districts, considerable epidemics of measles occurred after the assembling of the troops in camp. Such an epidemic occurred at Camp Pike, Ark., and the rapid spread of the disease was attributed to the fact that the rural individual was not immune to measles. At Camp Upton, New York, for instance, where troops were largely from New York City, the incidence of measles was low. However, in Camp Lewis, Washington, we also had a rural camp, the men being drawn from rural districts of the West. In this camp the incidence of measles was comparatively low.

In regard to our typhoid fever in the Army during the World War — most of the typhoid in the United States was sporadic. In France we had several small epidemics after the Armistice, due in most instances to an infected water supply. These epidemics occurred principally in November and December. Apparently the troops were heavily infected in the Argonne, where they drank water from shell holes in a country which had been fought over for 4 years. The troops were brought back to relatively crowded rest areas and carried the infection with them.

Dr. F. L. Hoffman.— Dr. Rosenau, in his very interesting paper, failed to touch upon a most important phase of the problem of seasonal disease incidence. I have reference to the effect of a high humidity coinciding with a high temperature. In an investigation which I made some years ago at Homestead, Pa., into the seasonal incidence of infant diarrhœa, I ascertained with reasonable precision the true effect of a high humidity closely coinciding with a high temperature.

We had about 1,000 children under observation from birth and until one year of age, but unfortunately for our purpose the summer was one of exceptional coolness and the actual number of cases of infantile diarrhœa was relatively small. But such as were brought to our attention by the attending nurses proved, with few exceptions, that infantile diarrhœa occurs in serious form primarily when the temperature excedes 70° and the humidity 80°. I speak from memory for I, of course, do not have the data with me, but they were presented in a fairly extensive form on the occasion of the last international conference on maternity held in London.

It would be difficult to exaggerate the practical importance of this conclusion, for it should not be difficult to perfect methods of weather forecasting to such an extent that the population concerned would be informed of the approach of conditions obviously inimical to infantile life. I may say in this connection that we had self-recording instruments in every home, so that the facts of the case are beyond dispute.

My investigation absolutely convinced me of the supreme importance of seeing that the room in which infants are kept is in a cool condition, and that the air is constantly in motion. With modern electric fans this should not be difficult, even in the homes of the poor. Only those who have visited many homes during the hot summer days can appreciate the almost unbelievable conditions under which little children are made to suffer the truly dreadful results of a high temperature coinciding with a high humidity. In the Tropics this conclusion should prove of especial value.

Sir Leonard Rogers.— He said that he would like to point out that Dr. Bellew about 1881 published extensive Indian statistics to show that there was a great tendency for cholera to run in cycles of 3 yearly periods, in much the same manner that infantile paralysis does. The speaker had examined the Indian statistics for 3 decades subsequent to those dealt with by Dr. Bellew, and found that the same tendency persisted, the incidence usually being slight in the 2 years following an epidemic year, after which, if the seasonal conditions and humidity were favourable, another year of high prevalence usually occurred.

Dr. Milton J. Rosenau (Closing the Discussion of His Own Paper). — I am glad that Professor Newsholme brought out some very interesting and stimulating suggestions, and that I have a chance to speak regarding them. In his long and useful contribution which he has made to this and other phases of epidemiology, he has often shown correlation between the prevalence of disease and environmental factors, and he is almost the only one who has not been led into the mistake of correlating unusual prevalence or absence of diseases with the conditions which occurred at that particular time.

Now it is almost inconceivable that the amount of seasonal diseases which we have at certain seasons should be very greatly influenced by the temperature or humidity. Just as with the corn crops, etc., we have sometimes bumper crops and sometimes poor ones, which are not the result of that season's conditions, but the cumulative effect of 2, 3, 4 or sometimes 5 years of previous conditions which have added to these results,— and so, unless we study disease in that same sense,— with a broad perspective — I think we shall often be led into error.

I thank Sir Arthur Newsholme for bringing out this particular point.

During the last great epidemic of influenza various methods were used to control the disease. One in particular which I think of was to use face masks, a safeguard introduced in San Francisco, and the word came back all over the country, and perhaps was cabled abroad that the way to control influenza was by the use of masks — every one should wear a gauze mask over his face up to the eyes. These measures were introduced on the down trend of the curve — anything you do at that point of the curve is bound to have good results.

One of the most illuminating evidences of seasonal prevalence of disease, occurred two summers ago in Russia, where typhus was prevalent everywhere during the cold weather and where, without any efforts at control having been made, it normally declined and disappeared as the warm weather came on. Then, as typhus

disappeared, cholera set up afresh, and, I may say, independently of water supplies, and was endemic throughout the entire Soviet Russia section during the time that I was there. That again disappeared in the autumn and typhus would come again. That is the sort of thing we see frequently repeated.

I want to express my appreciation to Professor Kofoid for bringing out the fact that the diseases we have to deal with are not simply mechanical invasions of parasites into a host, but are living reactions of life, and I think if we take the broader biologic view of disease we shall have better health administration in the Tropics and elsewhere.

Major Dunham's remark regarding measles was very interesting. I am glad he spoke as he did. This is one instance of the change of seasonal prevalence of disease as the result of man's conscious effort — so that we do control these things to some extent. In Albany, for example, when they drank badly infected water from the Hudson River there was a great deal of waterborne typhoid fever; there was more in the spring and fall than in the summer. When the drinking-water of Albany was purified the result was a great diminution in the amount of typhoid; and in coming down, the seasonal curve was reversed — what was left was summer typhoid, and practically none in the autumn and winter.

I want to also thank Dr. Hoffman for his emphasis on the effects of humidity, as well as temperature, as one of those elements of the weather which affect us. While I have always understood that cold is tonic and heat is enervating, we all feel that Dr. Deeks has given us a revelation in our experiencing the climate of these Tropics in the summer, because the heat and humidity of Jamaica have not had that effect.

THE RELATION OF THE MALARIA-CARRIER TO MALARIA PREVALENCE

C. C. Bass, M.D.

The purpose of this paper is to recall to attention certain well-known facts and principles underlying the transmission of malaria; and especially to emphasize the importance of the malaria-carrier as one of the essential and controlling factors in the spread and prevalence of the disease.

Numerous attempts have been made to transmit malaria to different experimental animals, both by direct inoculation with infected human blood, and by allowing infected anophelines to feed on the animals. Barring a single exception, all such attempts have failed. In this exceptional instance, Mesnil and Roubaud[1] succeeded in infecting a chimpanzee with benign tertian parasites. After an incubation period of ten days, the parasites were found in the blood for a period of ten days, after which time they disappeared. I[2] have shown that Plasmodium vivax and Plasmodium falciparum not only do not infect monkeys (*Macaccus rhesus*), guinea pigs, and rabbits, but that these organisms cannot live and grow in vitro in the blood serum of these animals, as they readily do in the blood serum of man.

Notwithstanding countless examinations of the blood of such domestic and other animals as might possibly be malaria-carriers and sources of infection to man, no animal has ever been found infected with a species of plasmodia identical with those that infect man. Malaria plasmodia are so easily recognized in blood specimens that we may feel quite certain that if any of our domestic animals were infected — and especially if they were important malaria-carriers — somebody would have found the infection in the course of examinations made for other purposes, if not during the numerous examinations made especially for malaria. It

[1] Mesnil, F., and Roubaud, E.: "Sur le sensibilité du chimpanzé au plaudisme humain." *Comptes Rendus des Séances de l'Academie des Sciences*, 165, No. 1, 1917, p. 39

[2] Bass, C. C.: "Studies on Inoculation of Experimental Animals with Malaria." *American Journal of Tropical Medicine*, Vol. II, No. 2, March, 1922, p. 107

seems reasonable to conclude from these facts that there is no malaria-carrier besides man, to be considered.

The term, "malaria-carrier," conveys somewhat different meanings to different people. Some may think of a malaria-carrier as being only a person having gametocytes in his circulating blood, and therefore presumably capable of infecting anophelines; others may consider a carrier as a person having parasites of any kind in the blood; others may define a carrier as a person who has latent infection, but who does not necessarily have any parasites in his blood at the time, although he may have them at some future time; and still others think of malaria-carriers as only infected persons without clinical symptoms.

Any person who has any malaria parasites in him, whether in the bone marrow, spleen, or circulating blood — however small the number — may later have much larger numbers in the circulating blood. The influences that control the multiplication of malaria parasites within the body are not definitely known. Neither do we fully understand those influences which control the production and the longevity of gametocytes, and their appearance in the circulating blood. Nor are we able to predict the course of events, in this regard, in any given case.

Given a person with the smallest possible number of parasites, perhaps all lodged in the bone marrow and the spleen, and none to be found in the circulation, there are a number of possibilities:

1. The parasites may all die, and the infection may disappear.
2. After a period of variable duration, the parasites may multiply until they are sufficiently numerous to be found in the peripheral circulation, and possibly to cause clinical symptoms.
3. The parasites that appear in the circulating blood may be asexual parasites (schizonts) only, and therefore not infectious for anophelines.
4. Both schizonts and gametocytes may appear in the circulating blood, in which case the blood may be infectious for anophelines.

5. The number of gametocytes present may, or may not, be sufficiently large for there to be any reasonable chance for anophelines that may feed on the carrier, to become infected.
6. The gametocytes may not be able to infect anophelines, because of some unfavorable condition or quality of the blood or of the parasites. This phenomenon has frequently been observed, although it is not well understood at present.
7. The gametocytes may be sufficiently numerous, and conditions may be sufficiently favorable, to cause infection of part or all of the anophelines that feed on the carrier.

The only carrier who at the time is a source of infection to others, is the carrier who can infect anophelines. The carrier who has no gametocytes, and who therefore cannot infect anophelines, may at another time have many gametocytes and thus become infectious. We must therefore consider every infected person a possible carrier and therefore a potential source of infection to others, whether his infection at the time conforms with one or another of the several possibilities enumerated above. A non-effective carrier may become an effective carrier at any time, or vice versa.

In our work in Bolivar County, Mississippi, during the year 1917, we examined 45,889 blood specimens. Of the tertian infections diagnosed, gametocytes were recognized in 3.67% of the specimens. Of the estivo-autumnal infections diagnosed, crescents were recognized in 28.72%. The wide difference between the per cent of gamete carriers found in the two varieties may be attributable, to some extent, at least, to the greater ease with which crescents are recognized, and the difficulty of differentiating between tertian gametocytes and schizonts.

Although the percentage of gametocytes was as much as four times higher in the highest month than in the lowest, they were always present in a fairly large proportion of the positive bloods during every month of the year. It was a very common experience to find gametocytes in the blood of an infected individual at one time, and not at another. All this further emphasizes the fact that every malaria-carrier

should be considered a potential source of infection to others.

Since man is the only malaria-carrier, and since all malaria-carriers may become effective carriers at any time, it stands to reason that, all other things being equal, any reduction in the total number of carriers in a given area will result in a corresponding reduction in the amount of transmission that occurs. In any locality, every malaria-carrier who is cured of his infection, or who loses it naturally, reduces by one the total of malaria cases in the locality. If 50% of these carriers should be disinfected, the transmission and the prevalence of malaria would be reduced to the same extent. To whatever degree effective treatment of those who have malaria can be carried out, the prevalence will be reduced by just so much. Therefore, I believe there is no question but that providing effective treatment to cure infected persons should be considered an important part of every malaria-control program.

In conclusion, I wish to mention some of the recent activities, in this direction, in the southern part of the United States, where most of the malaria of our country is to be found. Most of what has been done has been along the line of educating the physicians of the country, and inducing them to treat their malaria cases more effectively, especially in so far as cure of the infection is concerned. A large percentage of the malaria-carriers of the country are treated by physicians at one time or another. If all who are treated by physicians were cured of their infection, there would be a corresponding reduction in malaria-transmission and malaria prevalence. The tendency of physicians is to treat symptoms and patients, instead of to treat the infection. This is all right in dealing with self-limiting diseases for which we have no specific, but not so for malaria. Often the treatment advised after the active symptoms have stopped is inadequate. As a result, the patient remains a malaria-carrier. This tendency to neglect the cure of the infection must be overcome by education.

One thing that has been done in this direction is this: The state boards of health in several of the states have appealed to physicians, by letter or otherwise, to give special attention to curing the infection in the cases of malaria that they treat. The boards of health usually call attention at the

same time to the Standard Treatment for Malaria, which has been adopted and is recommended by the National Malaria Committee. Although unfortunately such appeals are likely to be disregarded in most instances, there is abundant evidence that this and other propaganda work for the same purpose have brought about excellent results, and that now a very much larger proportion of the malaria cases treated by physicians are receiving effective treatment. In some states these appeals by the boards of health have been repeated several times, so as to be made the more impressive.

It is easier to teach the medical student correct methods than it is to induce older physicians to change their methods. In most, if not in all, of the medical schools of the South, for several years past, the Professor of Medicine, or some one else in his department, has given one or more lectures each year to the Senior students, on the Treatment of Malaria, emphasizing the Standard Treatment. In Tulane, and I know, in some other schools this is done in an especially impressive way. The students are told that one of the examination questions for graduation will be, "What is the Standard Treatment for Malaria?" and that only a verbatim quotation from the United States Public Health Reports, Vol. 34, No. 52, will be accepted as the correct answer to the question. Of course, the student merely has to memorize carefully, in order to pass this test, — but still the future doctor has learned impressively a method of treatment which, if followed, will leave few malaria-carriers among the malaria cases that he will treat.

A number of the state licensing boards have effectively coöperated, by asking this same question on their examinations for licensure. Some of them have asked the same question several times, — that is in successive years. I wish they all did it every time. It would be a good thing to see that the doctors licensed to practise in the South — where malaria is such an important disease — know and presumably will adopt a method of treatment that would cure the infection in their malaria cases, thereby correspondingly reducing transmission and prevalence.

It remains for the future to show what effect these efforts will have. It would be impossible to get exact figures at present, but my own observation leads me to feel very certain

that a much larger proportion of malaria cases receive effective treatment now than, say, ten years ago. Not only are physicians learning to treat their cases more effectively, but a great many laymen are learning the important fact that to get rid of malaria and prevent relapse, it is necessary to continue treatment for a long time.

SUMMARY

1. Man is the only malaria-carrier to be considered.

2. Any person infected with malaria, irrespective of the number of parasites present at the time, may become an effective carrier, and therefore should be considered a potential source of infection to others.

3. All other things being equal, the malaria-carrier bears a direct relation to malaria prevalence. Any increase or decrease in the number of carriers should result in a corresponding increase or decrease in malaria prevalence.

4. Some of the activities in the southern United States, looking toward reduction of malaria-carriers, are of real importance.

THE LOCALIZATON OF MALARIAL PARASITES IN MAN

William M. James, M.D.

Among the most striking features at autopsy, in certain malarial cases, is the so-called blocking of the cerebral capillaries, and even larger vessels, by infected erythrocytes. One can find field after field in which every intra-capillary erythrocyte contains a parasite, always in some stage between midgrowth and segmentation, and each tiny blood vessel seems choked with them. In many of these cases a coma of several hours precedes death, and this comatose condition has been attributed to faulty cerebral circulation due to the apparent blocking. The well-known feature of withdrawal of *Plasmodium falciparum*, the parasite of estivo-autumnal malaria, in the latter half of its cycle, from the peripheral into the internal circulation, was correlated with these findings, and it was supposed that some particular factor prevented the free passage of the infected erythrocytes through the cerebral-capillary circulation. This factor could not be the increasing size of the parasites, since they passed readily enough through other internal capillary systems, and the red-blood corpuscle infected with *Plasmodium falciparum* does not enlarge. Moreover it has been observed that prior to segmentation, frequently large numbers of *Plasmodium vivax* also withdraw from the peripheral circulation, and in all probability some of these must pass through the cerebral capillaries — certainly through capillaries elsewhere — notwithstanding the far larger size of this parasite. The hypothesis most generally accepted has been that some toxin of pernicious malaria exerts a specific action on the walls of the cerebral capillaries, softening the endothelial cells and causing the infected erythrocytes to adhere to the capillary walls. Conversely it has been held that in some manner the erythrocytes themselves are affected, and that because of this they fasten themselves to the walls of the capillaries and to one another. This latter hypothesis, however, does not take into account the fact that if it be true, blocking should

occur elsewhere in the capillary systems, since those of the retina and other specialized organs contain also very small terminal vessels.

Some years ago, in Ancon Hospital in the Canal Zone, at the request of Dr. W. E. Deeks, then Chief of Medical Service, I undertook a comparison of peripheral blood films with smears from internal organs, in fatal cases of malaria. The object of this investigation was primarily to ascertain the effects of various methods of quinine administration in killing the parasites; also to find out whether there was a correlation between the clinical manifestations and the number and location of the plasmodia.

One of the first results of this study was to show that the so-called cerebral blocking occurred incidentally, and by no means regularly, in those cases that had a fatal termination; and cerebral localization could not be predicated from the antecedent symptomatology. Cases terminating in coma might or might not show the choked capillaries, and in some of these cases parasites could be found only with difficulty in the capillaries of the cortex, though they were abundant elsewhere.

These facts held good also with respect to cases dying in delirium. The cerebral capillaries might contain very few erythrocytes, or they might be very greatly congested; and in either instance the proportion of infected corpuscles was so variable that no definite correlation between symptomatology and parasitical localization could be determined. Dr. H. C. Clark, then pathologist at Ancon Hospital, pointed out to us that in other diseases with fatal termination, congestion of the cerebral capillaries occurred to the same degree as in some cases of malaria. We verified this by examining brain smears from all autopsy cases.

In some instances there would be a very general distribution of the parasites; the brain capillaries, the spleen pulp, the circulation in the liver and kidneys, and the bone marrow, all showing a heavy infection, with or without a corresponding degree of infection in the peripheral blood. In other instances there would be a marked preponderance of infection in some particular organ or locality, notably in the spleen or the rib marrow. I wish to note here that the rib marrow especially seems to be the site of election for the

development of the gametes of *Plasmodium falciparum*. Gamete forms in all stages of growth are frequently localized here, even when found scarcely or not at all in other places. They do not occur in the cerebral circulation, and rarely are found in smears from other organs, except those from the spleen. Only once have I seen them in any number in the peripheral blood, and that was in the case of a three-weeks'-old negro baby, smears from whose peripheral blood, bone marrow and spleen contained innumerable parasites of the species *Plasmodium falciparum* in all stages of the sexual and asexual forms. There was also a congestion of the cerebral capillaries, but with very few infected erythrocytes. The selection of the internal circulation for the development of the asexual forms of *Plasmodium falciparum* — as contrasted with the numerous occurrence of these in the peripheral circulation in infections with *Plasmodium vivax* and *Plasmodium malaria* — is one of the most striking phenomena in the localization of that parasite. So rarely, indeed, are these developing gamete forms found in smears from the peripheral circulation, that they have frequently been mistaken for cystic or other phases of the cycle supposed to be responsible for certain aspects of relapse, or the continuation of the life of the parasite during and after quinine treatment. I am sure these are the forms described by Craig and other authors as "resting stages."

Equally remarkable is the localization — in certain instances — of all the species, but particularly the asexual phases of *Plasmodium falciparum*, in the sinuses on the maternal side of the placenta. This may occur with or without a correspondingly heavy infection in the peripheral blood, but nowhere have I seen, except in the lumina of the cerebral capillaries, such an intense localization as I have sometimes found in placental smears and sections. Yet one may find a fairly heavy peripheral infection, and at the same time only very few parasites in the placental sinuses, as will be shown by Dr. H. C. Clark in the discussion of this paper. As compared in size with any of the capillary systems of the body, or even with the lacunae of the spleen and the bone marrow, the sinuses of the placenta are as the vast open spaces of popular Western cinematograph films to the confined cañon streets of lower New York City.

These facts render untenable any hypothesis that attributes cerebral localization to any change in the infected erythrocytes or the endothelial cells of the capillaries. Localization of *Plasmodium falciparum* in a particular internal organ is a shifting, and not a constant, phenomenon. It has its origin — as does the localization in general of the older forms of the asexual cycle in the internal circulation, and the developmental forms of the sexual generations in the marrow of the long bones and in the spleen—in biological peculiarities of the plasmodia, not in mechanical or toxic effects of these or erythrocytes or capillary walls. The symptomatology of malaria, particularly the striking coma or delirium, is to be attributed to the effects of the toxemia, not to circulatory phenomena.

Personally, I doubt whether a true cerebral stasis due to actual mechanical blocking, really occurs. Cerebral congestion undoubtedly takes place, but this may be seen with or without localization of parasites.

The localization of toxic effects during the course of a malarial infection, or later, is as interesting as is the localization of the parasites themselves. Years ago, Dr. Deeks pointed out the similarity between such localization and that seen sometimes in syphilitic infections. I once saw a case in which a very slight primary malarial infection was responsible for a softening of the spleen, with subsequent spontaneous rupture and almost immediate death from hemorrhage, — and, with great injustice to my late patient, I attributed the fatal outcome to a ruptured tubal pregnancy.

Various forms of cephalalgia, neuritis almost anywhere, painful livers or spleens, or both, are among the most common forms of localized toxic effects of malaria. These are often resistant to quinine administered by mouth, but disappear rapidly after a few hypodermic injections. They are probably due to the persistence of a latent infection, in which small amounts of elaborated toxic material are sufficient to work on an especially sensitive tissue.

DISCUSSION

Dr. J. W. W. Stephens (Opening the Discussion.)— The point that especially attracted my attention in Dr. Bass's paper was his statement in regard to the gametes in simple tertian. I have al-

ways found gametes in simple tertian infections, from the moment I recognized that the patient was infected.

In regard to the crescents in *falciparum* infections: Many of these do not show any crescents at all in the fortnight, three weeks, or perhaps longer period, during which the cases remain under observation. The reason for this is unknown.

With reference to Dr. James's paper, I think, speaking broadly, I agree with what he said, although I have made no special study of the conditions he described. I would only say that in estivo-autumnal malaria, fatty degeneration of the endothelium is apparently a well-recognized condition in the cerebral capillaries, but I do not know how far it exists in other parts of the body.

Dr. Herbert C. Clark. — I believe the malaria-carriers are more important persons in a community than the cases which come to the hospitals and the dispensary for treatment. Our labor camps in Honduras will show a range of 14 to 63% of individuals who harbor malaria parasites, and yet are able to pursue their duties as laborers. We are just starting a campaign of camp treatment, and special attention will be given the women and children. These people form dangerous disease reservoirs. They do not in many instances develop a true malarial attack unless they are sick from some other cause or receive a serious injury. Late stages of pregnancy bring out an attack in some of the women.

During all of last year (1923) we attempted to carry out the routine examination of placental blood-films for malaria. The technicians were new at this class of work, and the net findings were but 18% positive in the cases of normal pregnancy. During this year I have taken personal charge of these examinations and have studied the peripheral blood at, or very near, the time of the labor. This offers a pretty fair opportunity to study the localization of parasites, since the placenta in the late stages of its development is not very unlike the conditions found in the blood channels of the rib marrow and the spleen.

Up to date these examinations give the following results —

Positive mother's peripheral blood (thin film)	12.9%
Positive mother's peripheral blood (thick film)	22.5%
Positive placental blood-film	48.3%

The size of the blood channels in a placenta during the late months of pregnancy is enormous when compared to the capillaries of the brain and other specialized organs, yet these placental lacunae are favorite places for malarial parasites to collect and develop. This would seem to completely rule out the old idea that parasites localize in the capillary systems that are small

enough to ensnare the infected red-blood cells. The viscid property of the parasite and the infected cell is also hard to correlate with the condition found in the placental channels, since they are not necessarily arranged in a mural manner but are evenly scattered throughout the channel.

The localization of parasites would appear to be due very largely to the degree of stasis found in any capillary system. Fatal cases of malaria usually show a pretty general dissemination of parasites in the organs, but my autopsy experience, particularly in cases that have been treated vigorously a day or so before death, leads me to seek the parasites in the rib marrow and spleen, as well as in the brain capillaries. The rib marrow appears to withstand post-mortem changes a little longer than the other tissues, and marrow tissue gives a cleaner field of cells to study. I think I am safe in saying that an extreme localization of parasites in the brain capillaries does not occur in more than 15% of the cases which die after admission to the ordinary hospital. On the other hand, untreated fatal cases are sure to show vast numbers of parasites in the brain. The stagnant channels, like those of the rib marrow and spleen, are the difficult places to reach with treatment and are, at the same time, the favorable places (stasis) for the parasite to develop.

The discussion of the localization of parasites in man, these days, leads me into considerable confusion, because there is a parallel disease in cattle (*piroplasmosis*) that upsets all the conclusions I ever reach regarding the subject. The parasite of *piroplasmosis* (*Piroplasma bigeminum*) is of course found everywhere in the carcass when the acute disease is present, but one can examine for hours the blood and the blood-forming organs in a carrier of the disease, without finding a parasite. All the steers killed in the Panama City slaughter-house are carriers of this disease — which can be proved by inoculating their blood into non-immune animals. Yet the only practical way of finding the parasite in these carriers is to prepare a brain film for examination at the time such an animal is slaughtered for beef. The *brain capillaries in this instance* are the one place in the body where it is easy to find infected red cells. Some of these animals show an astonishing number of parasites in this location for animals that are apparently in splendid physical condition at the time they are killed.

This raises the question of the relative importance of parasite toxicity and parasitic thrombi in coma. I have seen members of a clinical staff follow a case to autopsy with the firm expectation of seeing a brain with the capillaries blocked by parasites, and yet very few capillaries contained infected cells. On the other hand, well-filled capillaries have been found in cases with little evidence

of cerebral irritation. No one can doubt, however, that some cases do die with a serious blocking of practically all capillaries and with capillary hemorrhages in both the white and the gray substance of the brain.

Dr. Aldo Castellani. — He congratulated Dr. Bass and Dr. James for their most interesting papers, and stated that he was in complete agreement with Dr. Bass that there was only one carrier of the malaria parasite — that is, man.

Dr. Castellani continued: It is interesting, however, to note how many of the lower animals, as well as the domestic animals, harbor parasites that, morphologically, cannot be distinguished from those of the human malaria. In Ceylon I came across several cases of dog malaria (*Plasmodium canis* Castellani and Chalmers), which is morphologically identical with the benign tertian malaria of man. Inoculations into monkeys were negative.

As regards the Standard Treatment mentioned by my friend, Dr. Bass, I agree with him that this method of treatment is highly valuable, and cures a very large number of cases. In my opinion, it might perhaps not be quite so effective in certain very serious cases who contracted the disease in Macedonia and certain parts of Africa and India. In such cases, administration of 30 grains of quinine for 4 days, and then 10 grains at night for 2 months, will not always cure the infection. In these severe cases 30 grains a day must be continued for at least a month, then 15 or 20 grains for 3 months or more. In many cases of malaria it is easy to obtain a clinical cure, but it is difficult to obtain a complete sterilization. The patient feels well, but that does not mean that the malarial parasite is not present. Sooner or later, the old malaria may flare up again. I have seen cases having relapses in England 7 or 8 years after leaving the Balkans.

As regards Dr. James and his interesting observations on the localization of the malaria parasites, I may mention that according to my experience localization of the malaria parasite may take place in very many organs — for instance, in the appendix. While in Serbia during the war, a patient was admitted to a Serbian hospital, showing the symptoms of acute appendicitis. He was vomiting and had severe pains in the right lower abdomen, and the muscles were contracted and hard. The medical officer made the diagnosis of appendicitis and called in a surgeon, who said it was necessary to operate immediately. I was working in the hospital next door, and I was asked to see the patient. He had all the appearances of having appendicitis, but he had a slightly enlarged and tender spleen, and I came to the conclusion that it was a case of appendicular syndrome, of malarial origin. The surgeon, however, insisted on operating at once. The appendix was removed,

and there were signs of only slight hyperanemia. After the operation, the second day, the patient felt well. On the third day all the symptoms of appendicitis appeared again, the patient vomiting and again suffering very severe pain in the right lower abdomen. The examination of the blood showed presence of malaria parasites. Quinine was administered — an intramuscular injection of 15 grains of quinine at once, and then 10 grains by the mouth every 4 hours — and all the symptoms of appendicitis disappeared permanently.

Dr. F. Fülleborn. — There is no doubt that Dr. Bass is quite right in stating that sterilization of the blood of the malaria-carriers by a sufficiently long quinine treatment must prevent the mosquito infection, and in consequence human infections with malaria. Robert Koch especially has insisted on this method of fighting malaria, but the results of an extensive experiment about twenty years ago, carried out during a period of several years in Daressalam, East Africa, were not favorable. Koch was not successful, in spite of the fact that he did not restrict himself by treating only the clinical cases of malaria until they were free from gametocytes. He also treated the much larger number of apparently healthy carriers in the same manner. The latter were detected by many thousands of systematic thick-film blood tests taken from the whole native population. It is true that a number of them were perhaps not treated because of the fluctuation of the population and the fact that the natives, suffering only very little from the malarial infections, did not like to take the bitter medicine.

There are very many apparently healthy carriers, not only among the natives of tropical countries, but also among the residents of temperate climates. For instance, Mühlens found in villages near Hamburg about one-third of the school children with tertian gametocytes in the blood, in spite of the fact that for a long time very many of these children did not have a history of any fever. It seems to us that a great deal of the malarial infection is spread by such children, who are seldom treated with quinine; and therefore in Germany we systematically treat with this drug all the school children carrying malaria parasites. This can very easily be managed by the teachers. During the World War, when the German soldiers in Macedonia were using quinine prophylaxis, for these reasons I confined quinine prophylaxis of the civilian population entirely to the children, and the mothers were quite satisfied with the results. I think that in treating with quinine only the clinical cases of malaria, until the gametocytes have disappeared, and not finding out and treating the *latent carriers* also, the results, so far as the diminution of malaria is concerned, will in many cases not be very satisfactory.

Dr. H. R. Carter. — What I know of the modern treatment of malaria is practically "second-hand." The determination of the prevalence of carriers in the Tropics — that is, people infective or potentially infective to anopheles — we tried out in a small way, in Panama. Dr. Kendall examined at several stations the blood from people who were well. The adults were well enough to work; the children were well enough to go to school. A summary of Dr. Kendall's results taken all together, showed that he found 78% infected. As to the children alone, he found 86% of them infected and, strange to say, he showed that one or two degrees of elevation of temperature might exist in such children while they played about with the others, without knowing they were sick.

There was nothing new in finding parasites in the blood of men or in children who apparently were perfectly well — that was an old story, even in 1904. When Kendall made these examinations, the novelty was in his finding children who had one or two degrees of elevation of temperature, yet who evidenced no symptoms of illness.

I do not recall any systematic attempt on the Isthmus, to cure our malarial cases of *infection*, as distinguished from curing the *attack*. These cases were treated until the symptoms of malaria disappeared and until they had recovered their strength and sometimes longer, but they were not willing to stay in the hospital after this, and medication after they returned to work was difficult, and in general impossible to carry out. There were, doubtless, many relapses, but to distinguish between relapses and reinfections was not easy. It is a little strange, when one reads the history of these things, to find what a small dose of quinine in the hands of other people, especially people introducing a new method, will cure malaria! In the recent epidemic in southeastern Russia, reported by McKenzie, the treatment was 20 grains a day for a week, following that, 15 grains a day for 2 days a week, administered for 8 months! That is a better result than I have ever gotten in the *cure* of malaria.

I am inclined to think, as a result not of accurate numerical observations, but of general impressions and the work of others, that the cure of malaria is ultimately accomplished by the man himself, rather than by the physician.

What is disheartening is the reports made, during the World War, from Great Britain. Sir Ronald Ross edited them, as I remember, and some 15 or 20 methods were used for chronic cases in Great Britain, with results that were poor. He himself reported the treatment in France, with extremely good results, of two divisions of troops from Salonica. He gave quinine, of course, but in addition required light exercise and more than the usual amount

of food. And he took great care regarding the hygiene of his people. I believe that as important as administering quinine for the cure of malaria is to keep the man up to par, for then he will get rid of the last remnant of the parasites himself, the quinine having reduced them to this last remnant.

Dr. H. J. Nichols. — This question of localization of parasites, and the remark of one of the speakers as to comparing malaria to syphilis, suggests to me that I might briefly state what is the status of localization of parasites in syphilis. Localization of the parasites of syphilis has been a subject in which I have been interested for several years, and if it has any relation to the localization of malarial parasites it may be worth outlining. It is known that in about 20% of the cases, generally speaking, the brain becomes infected with the spirochaetes of syphilis. There is good experimental evidence that there are different strains of the spirochaete. We have at the Army Medical School a strain from the spinal fluid, which has been going 12 years, and that strain is more virulent than a great many other strains. If a person is infected with the more virulent strain, the percentage of brain localization will be greater than if he were infected with a milder type. There is good clinical evidence, also, that certain persons affected with the same strain have more nervous syphilis than others, so we have those two possibilities — but this is not taking into consideration the host, and it has been shown that members of the same family infected from different sources have the same nervous affection. We have therefore three different kinds of people: those with the resistant nervous system; those with the ordinary nervous system; and those with the susceptible nervous system; and there are possibly two or more strains of the organisms. Hence, interplay of these two factors will determine how much nervous syphilis there will be. For patients with a resistant nervous system, and infected with a mild strain, would have a much lower percentage. The subject is also complicated by the question of yaws. The problem of the spirochaete of yaws could be woven into this question. We have these pretty well recognized conditions in syphilis — at least, a variation in the strains and a well-known variation in the resistance.

Dr. Seale Harris. — There is a great deal yet to learn about malaria, but with the application of our present knowledge of the disease we may completely eradicate it from among the causes of mortality in any country. The Italian Government in 1900 awakened to the economic importance of reducing the amount of malaria in Italy. The Government itself began the manufacture of quinine, and also carried on a publicity campaign. In certain parts of Italy, where malaria was most prevalent, the quinine was

given to all the people. In five years the incidence of malaria was reduced to three-fifths of what it was formerly, owing largely to this administration of quinine.

I have been practising medicine in Alabama for thirty years. The first ten years was in a rural community where the population ratio — colored and white, respectively — was 6 to 1. I am quite sure that at least 75% of the population were infected with malaria. It has been very pleasing to me to note the reduction of malaria both in the State of Alabama and throughout the South. As Professor of Medicine in the University of Alabama, from 1906 to 1913, I used to teach the students that it was just as criminally wrong for doctors to stop quinine administration in the treatment of malaria when symptoms had subsided, as to discontinue the use of mercury and the iodides after the secondary lesions of syphilis had passed off. We used the Italian method — that is, we gave quinine, 30 grains a day, for a period of 3 to 4 days, until the febrile symptoms had subsided, and then 2 grains of quinine, 3 times a day, for 90 days.

It has for many years been a routine with me to examine the blood of every patient for malaria. While living in Mobile, in 1914, I went over the records of 500 cases, and, making allowance for all errors in examination, estimated that 5% of the patients in 1913 were malaria-carriers. It is to be remembered that those patients came to be treated for gastro-intestinal and nutritional diseases, and not for malaria. They were all adult, white patients.

Malaria may simulate any abdominal infection. Several patients who came to us for ulcer of the stomach had parasites in their blood, and treatment for malaria relieved the ulcer symptoms. Our patients now come from half a dozen or more Southern states and I believe that in our clinic less than one half of 1% of those patients have malaria. The health officer of Alabama estimates that in 5 years, in 16 counties in Alabama, there will be no malaria. He hopes to make malaria a negligible factor in Alabama morbidity, within the next five years.

The question of the personal hygiene of persons having malaria was mentioned by Dr. Carter. In a Southern hospital, a negro who had a positive Wassermann was told that he had syphilis. He replied, "Ah knows that Ah have dat but Ah am sick, too." These malaria patients are often sick, besides having malaria, and I think that one great fault with our system is that we find the parasites in the blood and give the patient treatment for malaria, but do not make a physical examination of the patient and do not investigate his nutrition. Often there are complicated conditions that lower resistance, and when there is lowered resistance it is

much more difficult to cure the malaria patient. Unquestionably, the radical cure of malaria will reduce the number of carriers, and thus play an important part in malaria-control.

Dr. R. C. Connor. — All of my experience with the treatment of malaria has been derived from my work on the Isthmus of Panama. And all of my time has been spent in the treatment of malaria — none in solving the problem of sanitation. There are a few definite points that I would like to see brought out in this conference. Among these is the question of securing definite information from experimentation in a place where malaria has been introduced, from a malarious country, to a country like England, where, I understand, malaria does not exist. Such information should include the facts regarding the dose of quinine and the intervals of administration, in order that we may arrive at a definite conclusion as to the amount of quinine necessary, in the majority of cases, to effect a cure.

As every physician who has worked in the Tropics knows, this definite conclusion is practically unattainable there, for the simple reason that no matter how intelligent the "relapser" is, that same individual will go back and get his malaria again just where he got it before. Many of our so-called chronic relapsers, I am very sure, are re-infected. I am not so pessimistic regarding the cure of malaria as are some of my friends. I believe that malaria is more easily cured than is generally supposed. Personally I have known of no relapse suffered by a person who has gone from the Canal Zone to the States, who has followed out the treatment which Dr. Bass has outlined here, and which we have carried out for four years in the Canal Zone. I don't say that relapses have not occurred but that they have not occurred to my knowledge. I have known patients with malaria who have gone to the States and had malaria and come back with it, acknowledging that they had not been properly treated.

As I understand this feature of the present conference, corporations and states in the Tropics desire an effective outline for treatment, reduction, and eradication of malaria with the least cost. Possibly it is up to us to say whether malaria will be prevented by a certain dose, given according to a simple method that the natives can understand. Evidently small doses administered as outlined by Ochsner are impracticable. We are not dealing here with the same conditions as those that obtain in the southern part of the United States. We are dealing with a constantly changing population. What we need is some outline whereby we can advise a certain dosage of quinine. True, a certain amount of effective work can be done by sanitary engineers, but the corporations are not as

rich as the United States, and they cannot spend what we did in sanitating the Canal Zone. They are here for a different purpose.

We need more definite data regarding the relapsers, including reliable information as to whether the relapsers were checked up; whether their disease was tertian at one period and the next time of another variety; whether their condition was considered a relapse or possibly a re-infection that could be traced to an exposure to malarial infection, at intervals, after the primary infection.

Sir Leonard Rogers. — Dr. Rogers said that in connection with Dr. Bass's remarks on campaigns to reduce malaria there was a question in which he had long been interested in India. Almost thirty years ago, he discovered a very close relationship between heavy rainfall, a rising ground-water level, and malaria in an Indian regiment. He also noticed that the number of cases of malaria during the healthy first half of the year was in proportion to the number of cases in the unhealthy second half of the year preceding; and that when the regiment was changed, the cases were in proportion to the numbers in their previous stations. Thus the facts provedt hat these were relapses, nearly all being benign tertian cases. In such relapsing cases, he said, he found it necessary to continue the use of quinine for several months to complete the cure.

He subsequently made extensive studies of the relation of rainfall to malaria incidence, in areas under different conditions, and found that in deltaic regions flooded during the rainy season, there was most malarial fever during years of low rainfall. For at such times there was a longer unhealthy "drying-up" period, conducive to malarial infection, before the minimum temperature fell below 60%, when the new cases rapidly fell. He suggested that unhealthy or epidemic malaria years might be foreseen, in many parts of India, in time to render possible special measures to provide treatment. Later, he suggested to the local governments of India that this subject should be further investigated.

"Colonel Christophers, I.M.S., has shown," said Dr. Rogers, "that the serious occasional epidemics of malaria in the Punjab could thus be foreseen, and are closely related to rainfall; and during the last two years Major Gill, I.M.S., has made forecasts of the prevalence of malaria in the Province — from four to six weeks before the height of the malarial season — which proved to be remarkably accurate. His forecast of last year predicted excess of malaria in one of 25 districts, and smaller areas along two rivers, all of which occurred." Dr. Rogers said that such forecasts make it possible to concentrate on the epidemic areas, any staff that is available and he ventured to hope that similar measures might be found of value in other countries.

Colonel B. K. Ashford. — Colonel Ashford stated that in Porto Rico the people of the mountainous interior have, as a rule, little malaria; and that it is limited to certain valleys, although some parts of the coast regions are heavily scourged. In Utuado, he said, only 3 cases of malaria were found among 10,140 people.

Dr. J. G. Thomson. — In listening to this discussion, I have been impressed with the use of the term, malaria, in a very general sense. We ought to remember there are three different malarial parasites — namely, the malignant, the benign, and the quartan. We know from our experience during the World War that, as shown in Liverpool and London, malignant tertian malaria responds to quinine, but that the benign form is extremely resistant. In considering the standard of treatment in any country, we ought first of all to determine the predominating type of malaria in that area. One of the first things I attempted to determine in Rhodesia, was the type of malaria that predominated. I found, to my astonishment, that over 96% of the cases were *Plasmodium falciparum*. This fact is most important, because *Plasmodium falciparum* is fortunately very responsive to quinine treatment. I feel sure that if, by anti-mosquito measures, we prevent re-infections most cases can be cured within from three to five weeks. If these cases do relapse, benign tertian is frequently the cause. We know that mixed infections, with more than one species of malarial parasite, are commoner than previously suspected.

As regards finding a method of treatment, in Rhodesia — where blackwater fever is common — I was greatly impressed with the necessity of adopting some standard method. Laymen will not treat their malaria properly. The patient takes a few doses of quinine, and feels better the next day, so he stops taking the drug, returns to his work, and takes no more quinine until he has a relapse. This form of intermittent treatment predisposes him to blackwater fever. I tried to impress the people of Rhodesia that they must take quinine every day, and continue doing so for several weeks. When invited to ask questions, these laymen asked me to give them a formula, the practice of which I thought would be effective. — The medical men of Rhodesia adopt many methods of treatment. There are many formulas, possibly all of them equally efficacious. — In the meetings that I held, I actually quoted the formula recommended by the American Commission, as a useful guide for the laymen.

Concerning the gametocytes of benign tertian, mentioned by Professor Stephens, — they seem to occur throughout the course of the disease. In Rhodesia and Africa, it is extraordinary how few adults show crescents. I found no crescents in the peripheral

blood of 100 adult natives examined. On the other hand, between the ages of one and ten years, I found that over 40% of the native children carried crescents in their blood. This is a problem of immunity, requiring further study. Using the method of Dr. Bass, I made 18 cultures from malaria. The most striking thing revealed by these films is that the parasites, when developed beyond the ring stage, tend to group together and stick to the endothelial cells. That explains why the parasites collect in the capillaries of the internal organs. A post-mortem examination of a coma case may show numerous parasites in the internal organs, but in some instances they are rare, and in others wholly absent.

Parasites occur in every organ of the body. It ought to be remembered, however, that post-mortem examinations may fail to show parasites that we know must have been present during the life of the patient. And, for this reason, deductions made from examinations of the tissues after death, may be entirely misleading unless correlated with blood observations during life.

Dr. J. R. Ariza. — Malaria is the principal disease occurring in Banes, the part of Cuba where I have been practising for the past twenty-two years. Every year, I have to treat, in the United Fruit Company Hospitals, an average of 1,000 cases of this disease. The estivo-autumnal malaria is the most prevalent form. Tertian malaria is not very frequent; and quartan malaria is so scarce as to be a curiosity.

I have found, in a large percentage of estivo-autumnal malaria cases, that this disease is not so amenable to the Standard Treatment of malaria, as described by Dr. Bass, and that larger doses of quinine, continued for more than three or four days, are necessary to control the clinical symptoms of this disease. As a routine treatment, we give to our patients 45 grains of quinine per day, by mouth, until the clinical symptoms disappear. On the other hand, there are numerous cases of this form of malaria that can be treated — so far as the controlling of clinical symptoms is concerned — with 15 grains of quinine per day, the results being exactly the same as with the full dosage. This has been proved to me by Dr. Cordes, a disciple of Dr. Fülleborn. These facts mean that there cannot be, in practice, a standard, infallible method of administering quinine in a really malarial country, and that practitioners therefore have to treat every case according to its own conditions.

Dr. J. W. W. Stephens. — As scientific men, we ought to define the problem as accurately as we can before we start. We should define the terms, parasites and parasitic rates. We should

define carriers, and possibly other accessory factors, — and then, when we shall have defined what the conditions are in any particular area, we shall have data that may possibly explain why success attends treatment in one area, but not in others.

To come now to the scientific question that has been debated this morning, as to the distribution of parasites, this opens a field concerning which there is much to be learned. Is the parasite extra-cellular at any time? Parasites have been described as being present in the tissues free from the red cell. In regard to the infection of the child through the placenta, are we to assume that there is always some rupture, or *is* migration of the parasites possible?

In regard to the distribution, the question rises, directly or indirectly, as to what is the nature of "malarial dysentery," "malarial appendicitis," and various "malarial nerve symptoms." Are these due to the malaria parasite? I don't think a definite answer can be given. The problem of distribution also is involved in the question of relapses. Where are the parasites, and how do they escape from all the quinine administered?

To come now to treatment: We were impressed with the view which has been expressed by several observers, that the patient to some extent immunizes himself. We made an experiment on some cases to see whether that were possible, but had to stop because we were afraid the cases would prove fatal before cure was effected. So far as we know, speaking generally it is impossible for the patient to cure himself without treatment.

But I might mention here, as showing the difference in different cases, that a few doses of quinine suffice to cure experimental (inoculated) malaria cases, but no amount of quinine would cure "war malaria." In regard to supplementary treatment, we got the best result in any of our treatments by using quinine and arsenic. As regards the prevention of relapses, our experience shows that intermittent treatment gives a better result than continuous treatment.

Dr. F. L. Hoffman. — It may interest those present if I relate very briefly my personal experience during a seven month's trip through the South American tropics. I entered South America on the west coast, and passed over to ranges of the Andean Mountains, commencing my tropical journey at Pongo, about 12,000 feet above sea level. From this point on I took daily a 10-grain dose of quinine, — that is, 5 grains in the morning and 5 grains at night. I continued this precaution practically throughout my entire trip and at Para, on the Atlantic side, as well as for several days thereafter at sea. Although I passed through numerous

villages, camps, and settlements highly infected with malaria, and though I was often in the presence of persons suffering seriously from the disease, I did not experience a single attack nor did I suffer a single hour of illness from any other cause whatsoever. My blood was examined at Manaos and found to be absolutely free from any parasitical infection. All of this remarkable immunity I attribute to the Standard Treatment for malaria, — a treatment that I used also as a means of malaria-prevention.

Dr. B. M. Phelps. — The method which we have used recently in the treatment of malaria is the following: 40 grains of quinine sulphate by mouth for 4 or 5 days, until the temperature has become normal; 20 grains per day for 6 days — this period covering the remainder of the patient's stay in the hospital; and 15 grains twice a day, 2 days a week, for a period of 8 weeks. Although this method usually results successfully in a clinical cure, in a few instances we have observed recurrences of malaria symptoms and the presence of parasites in the blood, in the midst of our "follow-up" treatment. On rare occasions, and for various reasons — such as acutely disordered stomach, and children's refusing to take quinine by mouth — we resort to administering quinine intramuscularly. During the past year we have encountered but one case in which the disease failed to respond to quinine given through the mouth or intramuscularly, but the response to quinine given intravenously was almost immediate.

Dr. H. A. Greenwood. — I feel that greater emphasis should be laid on the point that, upon discharging a patient recovered from acute malaria, physicians should give very explicit instructions to the patient as to the follow-up treatment to be self-administered, *i.e.*, the proper prolonged taking of quinine, in order that the patient may not become a carrier.

To that end, we have instituted a checking system as follows: The patient is given a card containing 2 sets or more of 31 small squares, each set numbered from 1 to 31; in the center of the card there are a line for the patient's name, a space for the date this treatment is begun, and another for date of termination. — Thus, the treatment, and the record of it, may be started on any day of the month and continued for two months, or more, as desired. These cards being checked daily, they are an excellent means of insuring that the patients take the quinine in the dosage and manner already determined. The card is punched each day in the square indicated for that date.

This method if properly used will make possible a marked reduction in the number of carriers in any camp or district.

It has also been used where quinine was being administered to a

new labor group, known to have come from a region which was heavily infected with malaria, and where the taking of a blood test previous to employment was not possible.

And may I venture to suggest a method of administering quinine in liquid form? I have found it particularly useful in the follow-up treatment of men whose work requires mental effort, as this method does not produce the annoying effects of cinchonism to the same degree as other methods of administering quinine. I refer to the formula of Dr. Sinton, of India. My experience has been that the patients are more willing to co-operate in this method than in any other. The formula, in other than its quinine content, may if necessary be adjusted to the needs of the individual patient.

Dr. C. C. Bass (*Closing the Discussion of his Paper*):—The statement made in my paper, regarding the incidence of malaria found in Bolivar County, Mississippi, apparently was misleading. What I referred to, was an examination of thick films made by technicians in the course of a malaria survey. The technicians were not in all cases supposed to be competent to differentiate gametes from schizonts, especially tertian, in these thick films.

I have been very much interested to hear Dr. Stephens and Dr. Thomson say that they find tertian gametes in all cases in which tertian parasites are found. Although we have always found the former present in quite a large percentage, I must admit that we have not recognized them in all cases. We shall have to go back and make further observations on this point.

Professor Fülleborn's discussion served to bring out one of those ideas which I believe are fundamental, relative to the use of quinine in the control of malaria:—*viz.*, that in any case in which you have to force the people to take quinine, you may be sure in advance that you will fail. Unless you can induce the patients to take the quinine willingly, you may as well give up, especially if as much quinine is required as we think is necessary in many instances.

There appears to be the greatest variation of opinion as to the treatment which can or cannot accomplish results. I am not prepared to say any treatment is effective, the world over, to any given extent. Our experience is limited to the southern part of the United States. We may be dealing, there, with a form of malaria milder than usual. I can easily realize that a treatment which is effective there, as well as in some other sections of the country, may not prove equally effective in other parts of the world, and certainly will not bring the results among a specially selected group of patients such as Dr. Stephens referred to.

My chief interest for several years has been the study of malaria; and a large amount of malaria, under treatment, has come directly or indirectly under my observation during that period. This malaria has consisted of the kind that prevails in the southern part of the United States; and in addition I have observed the disease as contracted by a number of patients coming to the port of New Orleans from all parts of the globe. The question whether or not 30 grains of quinine, daily, controls clinical symptoms, has been kept constantly in mind. One of my special efforts has been to discover cases which continue to have symptoms while taking 30 grains of quinine or more daily. During a period of seven years I have not been able to find a single such case.

As for the cure of the infection: If we take a group of 100 infected individuals and give them quinine in suitable amount for 3 or 4 days or a week, and then stop, most of them will relapse in due time. A considerable number, however, will not relapse, being cured of the infection by the few days' treatment. If we treat a similar group for 4 weeks with 10 grains or more a day, about 30 or 40% may relapse and about 60–70% will be cured. If we treat a similar group for 8 weeks, about 5–10% relapse. We do not cure more than 90 or 95%; it would take more than 8 weeks to cure 100%. To cure 100% of cases, it is necessary to continue treatment for at least 3 or 4 months. We have to choose between one extreme, of curing 100%, and the other extreme of curing too small a percentage to meet the needs. The period of eight weeks is selected as a happy medium.

There is no method of examination by which anybody, so far as I know, can determine which individual will require 1, 4, 8 weeks, or longer. If we were able so to determine, of course there would be good reason to employ individual treatment for each case. Under the circumstances, however, we must select a treatment known to be effective in a large percentage of cases.

We cannot examine the blood, or make any other examination, of any individual and determine whether that individual has been cured. Therefore, as I have said, I believe that for practical purposes the thing to do is to employ a method of treatment known to be effective in a large percentage of cases, — and the Standard Treatment is generally accepted as meeting this requirement.

Although it is a fact that the clinical symptoms in most cases of tertian malaria are relieved by relatively small doses, and most cases of estivo-autumnal require a relatively large amount of quinine, it would be confusing to have a special treatment for different varieties. No one can determine in advance which cases will require the most, or which the least. A method that is effec-

tive in a large percentage of cases is preferable to many different methods. For this purpose the Standard Treatment was proposed, and I feel sure it is proving adequate.

Dr. W. M. James (Closing the Discussion of his Paper). — Mr. Chairman, you will recall that when you presided, years ago, over our medical-society meeting in the Canal Zone, you said that if there were a lack of interest as to the program, we would include a paper on malaria, and thus be sure of a large attendance and an animated discussion.

In regard to the problem of the treatment of malaria, the principal requirement is to know what it is that you are trying to cure. What is it that you are trying to do? Are you trying to eradicate a systemic infection? Or are you dealing with the presence of parasites in certain parts of the body where quinine cannot affect them? Or are you dealing with quinine-resistant, or quinine-fast parasites? I do not believe in any resistant form peculiar to the infection. Neither at autopsy, nor in the peripheral blood during life, have I ever seen malaria parasites that could not be classified in the sexual or in the asexual cycle. Personally, I believe that relapse is due to the persistence of quinine-fast parasites. This is the same view taken, and first enunciated, by Dr. Marchiafava. With respect to the amount of infection necessary to infect the mosquito, permit me to recall the interesting experiments of Dr. S. T. Darling, in the Canal Zone, some years ago. By an ingenious system of weighing the mosquito before and after feeding, and at the same time counting the crescents in the peripheral blood, he showed that it took from 25 to 50 gametocytes to infect mosquitoes. My experience with tertian malaria is along the same lines as that of Dr. Stephens and Dr. Thomson. I find gametes in practically all cases of infection with *P. vivax*.

As regards the Standard Treatment of malaria, I can say this, — I was in Louisiana for two months during the World War, and met there many Louisianian physicians who were using this method, and who were satisfied with it. The consensus of opinion was that the method gave very good results. Of course, however, there can be no hard and fast rule for the treatment of all cases.

Dr. Thomson has asked, "Where does the supply of crescents which infect the mosquitoes, come from?" He has noted the absence of these crescents in the peripheral blood of adults infected with acute malaria, and the presence of those crescents in the peripheral blood of children infected with chronic malaria. With respect to this problem, I should like to refer to the work of his distinguished brother, Dr. David Thomson. The latter demonstrated very clearly the cycle of the developing crescents, and

showed that this development took place in from 9 to 12 days. In cases dying with acute malaria, the development of the crescents in the spleen and the bone marrow — mostly in the latter — is in proportion to the duration of the attack and the amount of treatment. This is all very clearly brought out by Dr. David Thomson, and it explains why crescents are so infrequently found in the peripheral blood in acute malaria, and so frequently discovered in cases of chronic malaria.

The development of the gametes in all three species is not affected morphologically by quinine. What happens is, that the source of supply is cut off, but those gametes that have already begun to develop from the asexual cycle will continue in their growth, irrespective of treatment. In my own opinion, the developmental cycle of the gametes in benign tertian takes 4 days, and in quartan 6 days, or double the period of the asexual cycle.

I am in agreement with those who state that the benign-tertian infections are more difficult to cure than malignant tertians. But in my experience the parasite that relapses the most frequently is the quartan; and quartan infections persist longer than the others, although the acute attack is easily controlled.

With respect to simulation of appendicitis in malarial infections, I have assisted in connection with two such mistakes, and I know how it feels to find a supposed appendicitis turn out to be a phenomenon in the course of a malarial infection.

When I spoke of localization, of course, I meant relative localization. This is with respect to where the greater number of the parasites are found. I do not mean that if there is a heavy localization in the spleen or in the bone marrow, some parasites will not be found also in the capillaries of the cerebral cortex. But the so-called choked brain is by no means a constant phenomenon. I have no doubt whatever that profound changes take place in the capillary walls, but I doubt whether these changes have anything to do with the relative localization of the parasite in the capillaries of the brain, at one time, and in the sinuses of the placenta, at another.

Also, I distinguish between localization of the parasites themselves, and localization of the toxic products of the infection.

Regarding parasites being free from the erythrocytes, I have very rarely seen this condition with respect to half-grown or adult parasites. I believe that such occurrence on the slides made from the peripheral blood, is accidental and mechanical. In sections from the tissues, stained with hematoxylin and eosin, it is very difficult to distinguish any detail, and trustworthy evidence of free parasites cannot be obtained. Smears from the tissues may

show such parasites, and sometimes do, but here also I regard this phenomenon as accidental or mechanical.

I have no reason to believe that, except in cases of accident, the parasites pass from the maternal to the fetal side of the placenta. Sections through the placenta show the enormous infection in the maternal sinuses, and a complete absence of this infection in the fetal sinuses. I have seen many cases in which mothers with heavy infections in the peripheral blood and in the placenta gave birth to normal children. There is, of course, possibility of a rupture that would permit the passage of parasites from the maternal to the fetal side, but this is not a normal happening.

Estivo-autumnal malaria, especially at term, is a very serious complication, which, if not promptly treated, often results in the death of the child, and frequently that of the mother as well.

I wish to take this occasion to express my appreciation of the very valuable paper read by Dr. Bass, who is so high an authority on all subjects connected with malaria. As stated, I fully agree with his idea of a Standard Treatment for the purposes for which he recommends it.

ADMINISTRATION OF QUININE IN ACUTE MALARIA

With Special Reference to the Value of Intramuscular Injections

N. P. Macphail, M.D.

Malaria is by far the most important disease with which we have to deal on the coasts of Central America, and the question of the best means available for its treatment is a matter of great interest to those of us engaged in medical work in malarial districts.

During the past ten years, in the Guatemala Division of the United Fruit Company, 53,683 people suffering from malaria reported for treatment in our dispensaries and out-patient departments; and of these 11,695 were admitted to the main hospital. To determine the best routine treatment to adopt has therefore been to us a very important problem.

Opinions are still divided as to whether the more soluble salts of quinine give better results in practice, than do the more insoluble preparations. Our practical experience in Guatemala has led us to believe that the results obtained in oral administration are practically the same whether we use the more soluble ones, like dihydrochloride and bisulphate, or the insoluble ones, such as the sulphate. It seems certain that the solubility of the salt used, and dilution of the solution employed, are more important considerations in hypodermic administration than when given by the digestive tract.

Preparations of quinine have been given by the mouth, rectum, intramuscular injection, subcutaneous injection, and intravenous injection.

In our earlier experience in the "Motagua" valley of Guatemala, before satisfactory sterile ampoules of quinine were available for intramuscular injection, we made extensive use of rectal injections, more especially in severe types of malaria in outlying districts and "sick-camp" work. In those milder infections where vomiting was present, a few doses by rectum were found useful until vomiting ceased.

Results were occasionally satisfactory, and in a few cases brilliant. So often, however, did we find tenesmus caused in an irritable bowel by the quinine solution — even when such preparations as the tincture of opium were added — and so often did we have reason to doubt the absorption of the quinine, that we decided the rectal route of administering quinine was not a valuable routine measure. With the introduction of satisfactory preparations of quinine in ampoule form for intramuscular injection, the rectal injection was abandoned in favor of the intramuscular method.

Injection of quinine solution into the deep subcutaneous tissues was tried in a series of cases, various dilutions being used. The clinical results obtained were mainly satisfactory, certainly more so than when the dose was given by rectum. We found, however, that necrosis and subsequent sloughing of tissue was more common, and much more serious, than in the case of intramuscular injection; while control of the malarial attacks was not any more satisfactory than that obtained by the intramuscular method. We therefore decided that the subcutaneous injection had nothing in particular to recommend it as a routine measure. In our practice, therefore, the methods of routine administration of quinine are: Oral, intramuscular injection, and, when indicated, intravenous injection.

In the vast majority of mild infections we have administered quinine salts by the mouth. We had always been taught that during the febrile period better results are obtained by using quinine in solution than by using it in dry form.

The usual argument in favor of the solution is that during the febrile stage there is a scarcity of acid in the stomach, and therefore dry preparations are not so completely absorbed. Grosser has recently stated that the insoluble forms are completely absorbed during the febrile stage. With a view to determining for ourselves, if possible, the most satisfactory method of oral administration as judged by control of symptoms in acute malaria, we put a series of acute cases on liquid quinine grs. 20 a.m. and p.m. and a series on dry quinine, capsules, and friable tablets, grs. 20 a.m. and p.m. Our previous routine for years had been 15 grains in solution, 3 times a day. We have made an analysis of

approximately 3,500 cases for the purposes of reporting results. The charts chosen for analysis showed either positive blood-findings, as well as acute symptoms, or represented cases of uncomplicated clinical malaria, where histories and clinical symptoms, as well as the result of the therapeutic test, left no doubt as to the diagnosis.

The period covered was the past two and a half years at Quirigua Hospital. During this time there were 3,488 cases which were classified as uncomplicated acute malaria. Of this number 1,088, or 31%, were estivo-autumnal; 1,200, or 35%, tertian; 1,126, or 32%, clinical; and 74, or 2%, had a double infection.

There were 2,670 cases that were treated by quinine in solution grs. 15 t.i.d.; 661 by quinine in solution grs. 20 b.i.d.; and 157 by quinine in solid form grs. 20 b.i.d.

A total of 249, or a little over 7%, had secondary rises, persistent temperature, or other evidence of unsatisfactory control, found to have occurred following the various methods of treatment; 192, or a little over 7%, followed solution t.i.d.; 48, or a little over 7%, followed solution b.i.d.; and 9, or a little over 5%, followed the solid form b.i.d.

Of the 3,488 cases, 1,041 were of such a nature that quinine was given intramuscularly, one or more injections, as a matter of either primary or secondary treatment, in conjunction with oral administration of quinine. In other words, all methods of oral administration were protected by intramuscular injections of quinine, as required. Of the 2,670 cases treated by quinine in solution t.i.d., 901, or nearly 34%, were protected by one or more intramuscular injections. Of the 661 treated by quinine in solution b.i.d., 102, or a little over 15%, were protected by one or more intramuscular injections. Of the 157 cases treated by quinine in solid form, 38, or a little over 24%, were protected by one or more intramuscular injections of quinine.

These figures show that there were fewer secondary rises, persistent temperatures, etc. following administration of quinine in solid form. The figures also show that less protection by intramuscular injections was given to those cases receiving quinine in solid form, than to those receiving solution t.i.d. but a little more than to those given solution b.i.d.

While the series receiving quinine in solid form was a small one, it would appear that the results obtained from giving friable quinine tablets or capsules twice daily, compare favorably with results obtained by the giving of quinine solution either twice or three times daily.

Results from giving quinine solution b.i.d. in 20 grain doses, appear to be as satisfactory as those following three daily doses of 15 grains each.

The economy in work for the hospital staff, effected by giving the quinine twice a day is considerable, and if a larger series of cases prove that the solid form, given twice a day, brings as satisfactory results as those from the liquid preparations, one of the objectionable features of quinine administration is removed.

In the treatment of pernicious forms of malaria, to save life, quinine must enter the circulation as rapidly as our available means make possible, and in these cases we must resort to the hypodermic needle. When quinine is administered intravenously its action on the parasites is undoubtedly much quicker than by any other method; and, as it comes immediately in contact with the parasites in the circulating blood, the results should be more certain and ought to be obtained in less time. One of the objections to the use of quinine in this form is, that its administration requires the services of a skilled physician in each case. In a large clinic, where a great number of the cases are first seen in outlying sick-camps and in dispensaries, it is practically impossible to arrange that all pernicious cases shall receive intravenous injections immediately. On the other hand, no time need be lost in giving an intramuscular injection. The alarming symptoms which we have occasionally met with, following an intravenous injection (especially in cases when the cardiac action is weak) and which no amount of dilution of solutions, slow administration of injection, or combination with stimulants seems to reduce or avert, — these alarming symptoms have been practically responsible for our deciding that intravenous injections of quinine should be reserved for special cases. To them it should be given slowly, in small doses, diluted to 1 in 200 or over, and it should be given only by a qualified medical man. We believe from experience that in pernicious cases, where the blood pressure is already low,

these precautions are very important. When one small dose has been administered in this manner, the after-treatment can be continued by intramuscular injection with, in our belief, equal benefit to the patient, a smaller danger of disturbing symptoms, and less trouble to the hospital staff.

After carefully trying out all methods, we have come to the conclusion that quinine administered intramuscularly meets practically all requirements for cases of acute malaria requiring hypodermic treatment. In most of the pernicious cases treated in our Hospital, sick-camps, and dispensaries, quinine is administered intramuscularly.

In previous years we used many home-made solutions, and later we obtained the soluble tablets of quinine hydrochloride and urea, all of which gave fairly satisfactory clinical results, but caused necrotic processes more frequently than the sterile ampoule preparations now in use. For the last few years we have been using: Quinine Dihydrochloride Ampoules — The Norwich Pharmacal Company, New York; "Empco Ampoules" Quinine Dihydrochloride — Marvell Pharmacal Company, New York City; and Quinine Bichloride Ampoules — H. K. Mulford Company, Philadelphia. These, and others that we have used also, have given us excellent results. The ampoules used contain 1 c.c. with 7½ grains of quinine in each, and are not diluted further. At one period we diluted the contents of the ampoules with varying quantities of salt solution, but no differences in results were apparent.

The technique that we recommend consists of complete asepsis, slow injection, and thorough massage. The dose used for adults is from 15 to 22½ grains, repeated as found necessary; but never should more than three injections be given in 24 hours. The site of injection should be so chosen that large vessels and nerves are avoided.

The usual objections advanced against the intramuscular use of quinine are: that absorption is rather slow; that injections are occasionally followed by necrosis of muscular tissues, with subsequent abscess formation, requiring surgical treatment; and that the process of healing is slow. On the other hand, it has this advantage: that any well-trained nurse or field dispenser, properly instructed in the technique can use this method of administration.

Regarding the slowness of absorption there can be no doubt, and, as suggested before, a small intravenous injection is indicated in serious cases of pernicious malaria, arriving in a hospital where medical men are immediately available. With respect to the necrosis of muscular tissue, our experience with many thousands of cases leads us to believe that necrotic processes of any importance are comparatively rare when the intramuscular injection has been carefully given by an experienced person.

We have analysed the charts of 1,134 patients who in the past two and one-half years have received intramuscular injections of quinine in Quirigua Hospital, and we find that a total of 1,952 intramuscular injections were given in this series. Of the 1,134 cases receiving injections of quinine, 1,041 were malaria cases, and 93 were other than malaria. The 1,041 malaria cases received 1,741 intramuscular injections, and the 93 "other than malaria" cases received 221 injections, as therapeutic tests. The number of injections given to individual cases varied from one to 14. Of the above number 11, or .5%, developed necroses and subsequent abscesses, which required surgical incisings. Three of these cases developed double abscesses — or 14 in all. Of the 11 necroses, 5 were in cases other than malaria, 3 of which were of such a severe nature that death ensued; 3 of the necroses were in babies of low vitality and low state of nutrition.

The above percentage is probably high, as representing our recent experience regarding the incidence of necrosis following intramuscular injections of quinine; for it does not take into account the large number of injections given by our field dispensers, in which instances no necrosis occurred. Or, if it did occur, it developed after the case had been received in the main hospital and was there accounted for.

Two recent articles that I have read in the journals made a great point of the pain inflicted on the patient in giving intramuscular injections. Our experience, on the contrary, has been that it is rarely complained of, and the average patient is quite as willing to have an intramuscular quinine injection, as he is to take a dose of liquid quinine.

The results we have obtained from the intramuscular use of quinine have justified us in believing that this method may be recommended; that it has obtained a permanent place in

the handling of pernicious cases of malaria; and that it is also a valuable aid to oral administration in the more persistent types of benign infection.

I would like to place specially strong emphasis on the value of this method in outlying camps and districts patrolled by dispensers and camp runners, who have been thoroughly trained in giving quinine injections.

In our dispensary districts, 20 to 60 miles from the Hospital, the application, by dispensers, of intramuscular quinine in pernicious cases has undoubtedly saved very many lives. It is not often, in strictly medical practice, that we are justified in taking credit to ourselves, or giving it to another, for saving a life. In comatose cases, and in some of the many other types of pernicious malaria, in remote districts, we need not hesitate to give full credit for a life to the field dispenser who succeeds in getting sufficient quinine into the patient's circulation early enough to save that life, for all those cases mean certain death to the patient unless quickly and efficiently attended to.

CONCLUSIONS

1. For oral administration, the more insoluble salts of quinine give as good results as those more soluble.

2. For subcutaneous, intramuscular, and intravenous administration, only the more soluble salts of quinine need be considered.

3. Quinine administered twice daily gives as satisfactory results as when administered three times daily.

4. It appears, from the analysis of the small series of cases in which quinine in solid form was given, that this method of administration compares favorably with that of quinine in solution.

5. The intramuscular injection of quinine is an efficient and practical method of quinine administration.

6. The danger of tissue necrosis incidental to the intramuscular injection of quinine, is small and insignificant, when we take into consideration its life-saving property.

DISCUSSION

Dr. Charles C. Bass (Opening the Discussion). — One of the questions that arise in connection with Dr. Macphail's paper is the relative value of soluble and of less soluble salts of quinine, when

given by mouth. We have had a rather large experience, in which we gave two different soluble salts, and also ordinary sulphate in capsule form, to a large group of prisoners. So far as possible, they were divided into comparable groups. After some 4 or 5 months of experimenting with about 600 people, we came to the conclusion that, although we were not prepared to say that some of the soluble salts might not be as effective as the sulphate, we had found no evidence proving either of them to be the more effective. As a matter of fact, the figures were actually in favor of the sulphate — an indication that was in line with the experience of Dr. Macphail, described in his paper.

With respect to the administration of quinine hypodermically, or into the tissues, I must confess that my experience has been rather limited, and that perhaps I may be somewhat prejudiced against this method. One who has seen quinine given hypodermically or intramuscularly, in many instances, and by many different physicians, gets a more nearly correct impression as to unpleasant results, I believe, than one is likely to get if he does it all himself. The large number of abscesses, and the damage to the tissue, that occur in a large percentage of cases when the injections are made by many different doctors and nurses, is very impressive. It certainly has been quite impressive to me.

Although some of those who enthusiastically employ the method do not see any abscesses or other unpleasant effect, many others have entirely different experiences. A remedy or a method that is harmless in the hands of a few especially competent individuals, but the opposite in the hands of many others, is not appropriate for general use. It is all very well for one to say he never discovers abscesses; others do find them, and some find many.

Another impressive test can be made by giving quinine to experimental animals, and then, at any suitable time, opening up the tissues and seeing what the results are. The severely damaged, if not necrotic, tissue that is found shows at once that this is quite a formidable procedure.

Observation relative to hypodermic or intramuscular administration of quinine, chiefly by other people than myself, and observation of animals into which quinine had been injected in different forms, and into different tissues of the body, lead me to feel that, before using this method, the doctor should take a few injections himself. I believe that such a precaution would lessen the enthusiasm of almost anybody for this method of treatment. The effect on the tissues of animals is so very impressive that one realizes at once that, although the measure may be justified in some cases, such cases must be extreme. I believe that better results are obtained by giving the quinine intravenously, even in these instances.

The only reason for giving quinine by either of these methods is to save a life which we believe would be endangered by waiting until the dose could be gotten into the blood by oral administration. It is certainly very indefinite as to when the patient will get the effect of quinine given intramuscularly. The effect of it administered in that way is not any more rapid than when given by the mouth — as a matter of fact, all experimental evidence indicates that it is slower. If the patient's life is in danger, enough quinine should be given intravenously to save him until he can take it by mouth. My own experience leads me to the conclusion that quinine given hypodermically or intramuscularly has little or no place in the treatment of malaria.

Dr. E. B. Ross. — I wish to go on record as agreeing with Dr. Macphail's paper in every detail. After 12 years of experience in the Tropics, we have settled down to a routine 45 grains of quinine a day for all ordinary cases of malaria. To the small percentage of comatose cases, as well as cases which, on account of vomiting, are unable to retain quinine by mouth, we routinely give intramuscular injections. To the very extreme cases we give an initial small dose of quinine, intravenously followed up by deep intramuscular injections until they are able to retain the quinine taken by mouth. Clinically, this method has proved of undoubted value, and we will continue it until somebody shows us a more satisfactory method.

Necrotic abscesses following intramuscular injections are so rare, when the injections are properly given, that they are not to be considered as a contra-indication. The greatest objection to the intravenous method is, that it requires a skilled physician acting under aseptic conditions, to administer it.

Dr. Aristides Agramonte. — I refrained from entering into the discussion of malaria this morning, for I saw that there was plenty of talent, and superior, to fill up the time, but since the treatment of malaria is a subject that we are all interested in, I will say something now.

When I was in conversation with one of our colleagues this morning, Dr. Azurdia, he remarked that in this connection a certain Spanish adage might be applicable, "Every Master has his own book to follow." That is generally true.

I desire to give my unqualified support to this paper by Dr. Macphail. I myself have had a little experience in the treatment of malaria — and I am not referring to the time of the Spanish-American war, but to the years that have gone since. — Unfortunately for us, in my country, we have had a great increase of malarial infection within the last few years, owing to the immigration of laborers needed for the cutting of cane at the time of the

yearly crop. This immigration consists mainly of men from Jamaica and Haiti. Needless to say, the immigration from Haiti is most undesirable, from a great many points of view. As to the immigration from Jamaica, it has brought to us a periodic increase in the incidence of malaria. We have demonstrated this as much as it can be demonstrated, for these immigrants bring the disease with them and then propagate it in the various parts of the island, particularly in the eastern and central parts. There they work, — 15,000 to 20,000 men yearly. Steps have been taken to offset this condition, but what I am trying to point out is that we have more malaria now than we had formerly. It is of the estivo-autumnal type, and extremely virulent.

There are cases of tropical malaria that allow no time to wait to give the Standard Treatment. This method is applied in the majority of cases, but each case must be taken "on its own merits"; and only from a sanitary standpoint can we rely entirely on the routine method of treatment. Whenever we are called to the bedside of a man who has been treating himself with small doses of quinine for a few days, and find that he is suffering from intense chills, is blue in the face, and either quite comatose or about to become so, we cannot use the Standard Treatment. We must administer quinine as quickly as we possibly can, and in as big doses as he can stand. That is the only way we can save his life.

In private practice, I have probably injected quinine intra-muscularly in about 100 cases during the last 4 or 5 years. When a patient has a high temperature, with chills and all the other symptoms of an acute attack of malaria, I usually do not wait to make a diagnosis. I take a blood film and give him an injection of quinine in the gluteal muscle. I use dihydrochloride salt, preferably, for this purpose. After that, there is plenty of time to institute a plan of treatment for the cure of the disease. I have followed this procedure without having any accidents. It is true, as Dr. Bass says, that other men have had abscesses produced. I think that by all means we ought to taboo subcutaneous injections, and practice only the intramuscular method or the intravenous, preferably the intramuscular.

If we carry out the following three measures in the administration of quinine in this way, I am sure that we shall not have any accidents: — first, use the proper salt; second, inject slowly; and third, massage thoroughly, easily, and for a long time, the region surrounding the spot where the injection is made.

Dr. J. W. W. Stephens. — This is almost an age-long controversy, and I do not wish to add any fuel to the fire. Very little is to be gained by one man's saying that a method is very good, and the next that it is very bad. — Our procedure, in ordinary cases, is to

give quinine by the mouth, or when the case is serious injecting it by way of the muscle, (into the deltoid) giving one gramme, and repeating the dose about four hours afterward if necessary. In my experience, we have had no unsatisfactory results. With respect to intravenous injections, our experience is that a series of six intravenous injections, of one gramme each, did not drive out the parasites, in a fair percentage of cases. It may or may not have any bearing on the question, but when quinine is introduced into the blood, it cannot be recognized there as such after one minute.

Dr. Roland C. Connor. — Our method of treatment has been practically on a parallel with the method described by Dr. Macphail in his paper. There is one favorable condition that obtains on the Isthmus — possibly owing to Dr. Deeks' efforts — and that is, we have a much better quality of quinine now. Formerly we got a very poor grade, in compressed tablets that were insoluble. We also had difficulty in dissolving capsules, a trouble which we thought possibly was due to a process in their preparation, such as hardening in formalin to prevent their disintegration in the Tropics. We subsequently administered liquid quinine, 5 grains to the teaspoonful. Most of our patients, who are old employees, will now ask for the continuation treatment in liquid quinine form. They think it is the best, and we thought so at the time it was instituted. But now in the hospital I often give capsules and tablets, which I am sure are easily soluble; the latter are freshly prepared and bring good results. In cases which we believe to be dangerously ill, and to whom we consider quinine should be administered otherwise than by the mouth, we often give it intravenously or hypodermically. There is one thing sure — you cannot depend on a doctor to give quinine intravenously unless he has been shown properly how to do so. The only accident I have had — and it was not a serious one — occurred once as I came to the bedside while a young doctor was giving the quinine intravenously too fast, and the patient collapsed. We have never lost a patient from accident, by the intravenous method. I admit that we do not have to give quinine intravenously or hypodermically in many cases; it is rather rarely now that we need to do so. Probably we have now only half a dozen nurses, out of 65 or 70 on duty at Ancon Hospital, who know how properly to give quinine hypodermically.

As I have said, my own experience is exactly parallel with that of Dr. Macphail. If I were in the same area as he is, I should not hesitate to order hypodermics of quinine, if my field men had been trained by physicians to give them intravenously, and if they were prepared to prevent any dangerous effects of intravenous quinine by being ready immediately with a stimulus, such as caffeine

sodium benzoate, to counteract the shock that, we find, does occur sometimes with intravenous injections.

Col. James Cran. — I have had an opportunity, on several occasions, of seeing the work that takes place in the Quirigua Hospital; and, although I live only a hundred miles from Dr. Macphail, there is a very marked difference in the material with which we have to deal. In the Valley of Motagua the vitality of the population is low, for various reasons. They are badly nourished, and their long years of suffering from malaria and hookworm have seriously affected their stamina. As a result, the resistance to any ailment is low, and one sees many forms of disease running riot there in a manner seldom observed among a population unaffected by these causes. A few years ago, it was nothing unusual to have in the hospital — all at the same time — a dozen cases in a comatose condition, and there I have seen brilliant results obtained from intramuscular injections of quinine.

I had the pleasure of watching six such cases at one time; five of those recovered, as a result of the intramuscular treatment. I know of no other method which could have saved their lives. Dr. Macphail has not included in his paper mention of the thousands of injections administered in the field by his dispensers, one of whom has given about 15,000 intramuscular injections, with practically no necroses resulting. The technique of today makes the pain negligible, and means that necrosis is almost unknown. In Belize we have a different race to deal with; there is very little hookworm (except among the Indians) and comparatively little malaria, especially in its pernicious form. Consequently, the resistance is stronger; and, since the treatment varies according to the patient and his resisting power, there is not the usual reason for the introduction of quinine in a rapid manner.

The relatives, it must be remembered, have to be considered almost as much as the patient himself — not only in comatose conditions, but also in those remittent cases with which private doctors have to deal, when the patient (especially if a young child) is running a high temperature for several days. The relatives are very much worried and want to know what kind of doctor it is who cannot cure malaria in a week's time. It is in cases like these in which I have found the intramuscular method very beneficial.

Somewhat over 20 years ago I gave my first intramuscular injection of quinine. In those days the preparations were not so good as they are now, being more irritating and insoluble. I had one patient, a robust woman, who had been running a temperature of about 104 for over a week; and I had tried, without any effect, all those methods of giving quinine which I had at my disposal. A

visiting doctor who happened to be present, had some of the hypodermic compressed tablets. At his suggestion I tried a 3½ grain dose, and the temperature dropped to 102. I gave another, in the evening and another next morning, when the temperature came down to normal and remained there. That woman developed a punched-out hole in the gluteus, but she was one of the most grateful patients I have ever had.

Another case — also a woman — was a native of the colony, who had spent about three years in the United States. Shortly after her return she developed a severe attack of remittent fever. This lasted for several days, in spite of quinine, given in the usual way; but after several intramuscular injections had been given, her temperature came down to about 100, remained there for a week, and then returned to normal, to stay.

Still another case was a child about 3 months old, in a comatose condition. I gave one intramuscular injection, of 5 grains of quinine, which was sufficient to relieve the condition, and to permit of administration by the mouth.

My experience indicates that intramuscular injections should be reserved for those resistant and pernicious cases in connection with which, either we have failed, in using other methods, or else those other methods are not available. My experience, also, has been like Dr. Macphail's in verifying the fact that because of the rapid results of intramuscular injections, patients do not consider any little discomfort which they may suffer from it. I would emphasize, that none of us believes in intramuscular injections as constituting a routine or elective method. In my practice I still continue giving quinine by the mouth — even when giving it intramuscularly — whenever the patient can take and retain it. There can be little doubt, however, that in those grave comatose conditions, which prove rapidly fatal in a debilitated constitution, the intramuscular or, if need be, the intravenous method is the only way to save lives. In fact, even in those less severe, but more protracted, cases in which the oral administration does not have the usual effect, the addition of a few doses intramuscularly undoubtedly hastens the relief of the clinical symptoms. Naturally, most of those who suffer from the disease, are anxious to obtain this relief as early as possible.

Sir Leonard Rogers. — For the last 20 years I have advocated the view that the vast majority of malarial cases yield, within 5 to 7 days, to oral quinine in doses of 30 grains a day; and that, in the more serious infections, intravenous injections are far more effective than intramuscular, and are quite safe if injected slowly. They leave very little necessity for the use of the intramuscular

method, in which the drug is absorbed slowly, as shown by the absence of cinchonism. The apparent failure of oral quinine to stop the fever in a very few days, was on one occasion — by analysing the solutions supplied by the hospital dispensary — found to be due to the fact that only 4 grains, instead of the 10 grains ordered, were put into the solution, the rest being stolen. That may account for intramuscular injections given by a medical officer giving superior results.

The difficulty is with pernicious cases, and with those that vomit orally-administered quinine. The former can sometimes be detected in time only by finding numerous parasites — nearly always malignant tertian — in every field of an oil immersion lens. Two such cases in which we advised intravenous quinine, but the medical officer would not allow it to be given, became comatose, one and three days after, respectively, and died in spite of large doses given orally. On the other hand, a patient admitted for cholera — collapsed and only semi-conscious — in whom 46 malignant tertian parasites for every 100 red corpuscles were found, had no cholera; recovered after one 15-grain dose of quinine bi-hydrobromide (which we found, by animal experiments, was slightly less toxic than the bi-hydrochloride), and three such doses intravenously on the following day; and he left the hospital in ten days.

Another method which I worked out during the World War, and which appears to me largely to obviate the disadvantages of both methods of injection, is the use of bi-hydrochloride of cinchonine in the place of the quinine salt. It is absorbed, when given intramuscularly, very much more rapidly than the latter salt, as shown by symptoms of cinchonism often appearing within half an hour. This we had never seen after quinine injections. Moreover, experiments on rabbits showed that, twelve hours after the injection, three times as much of the cinchonine salt had been absorbed as of the quinine; while at the end of three days, three times as much of the quinine was still unabsorbed in the muscle, — a large dose having been given. Also, in man far less pain and no induration is induced by the cinchonine salt. We have had several patients who have taken both forms of injection, and they have all testified to the fact that far less pain and inconvenience are suffered after the cinchonine-salt injection. That salt absorbed so rapidly as to be almost equivalent to quinine, given intravenously.

Most of our cases were benign tertian and further trials are necessary to ascertain if it is as efficacious as quinine administered intravenously in pernicious malignant-tertian cases. We give 10 to 15 grain doses in 1½ to 2 c.c., injecting them into the deltoid once a day, on four consecutive days, after which time bilious

remittent cases yield, and quinine can be continued orally.

All solutions for intravenous and intramuscular injection should be put up in ampoules and sterilized in an autoclave; thus, either salt will prove efficacious. There are, no doubt, conditions elsewhere such as Dr. James has met with, in which intramuscular injections are more convenient than the intravenous. But I hope he will make a trial of the bi-hydrochloride of cinchonine intramuscularly in the way I described.

Dr. F. Fülleborn. — In heavy cases of malaria I should not like to leave out the intramuscular injections of quinine. During the World War they were very effective, in Macedonia, saving many lives. The injections have also the great advantage that the physician can be sure the patient has the quinine in his body, and that it cannot be vomited. In Germany we prefer quinine carbamidatum (urethan-quinine) ready for use in sterilized glass tubes. With this preparation, it is only very seldom that we find disagreeable local reactions or necrosis of the skin.

Dr. Aldo Castellani. — It is with great pleasure that I have listened to Dr. Macphail's paper, and heard of the good results he has obtained from the intramuscular administration of quinine. This method should, of course, be used only in serious cases, — not in the ordinary, mild cases for which the oral administration would be effective. In the East, where I spent many years, the two principal objections brought forward against the use of the intramuscular method of quinine administration are, first, that it causes a great deal of painful inflammation and often abscesses; and second, that it may be followed by tetanus.

As regards these objections, I think that if the ordinary precautions are taken no accidents will happen. The skin should be disinfected with tincture of iodine, and a reliable preparation of quinine with urea should be used. Another precaution to be taken is never to give a second intramuscular injection in the same spot as the first. It is also important that the injection be made deep into the muscle, with a long needle, and not subcutaneously as always happens when a short needle is used. My usual procedure is to give quinine by mouth in ordinary cases, and by intramuscular or intravenous injection in serious or pernicious cases.

Dr. William M. James. — Regarding intramuscular use of quinine, I want to emphasize something of interest to parties going out into heavily-infected districts: —

Perhaps ten or twelve times a year we are consulted, in Panama, by parties that are going down to Darien, probably one of the greatest hotbeds of malaria to be found anywhere in the world. These people have been advised, elsewhere, merely to take with

them pills and capsules. They make the trip without any physician, go into the bush where the natives are all infected, and within four or five days members of the party succumb to fever. They cannot hold quinine on the stomach, and in a short time they come back to Panama ready for the cemetery. When one has seen these conditions in many instances, and has lost personal friends, he is particularly impressed by the fact that no one should go out into a heavily infected district, without a competent physician in the party, and trust to taking quinine by oral methods.

This is the especially valuable part of Dr. Macphail's paper: namely,

> "Of about 3,000 patients, 1,000 patients were treated intramuscularly because they could not take quinine by mouth."

There is no such thing in my experience as a death from quinine, when the drug was properly given by intravenous or intramuscular injection.

The problem of the United Fruit Company is this: — They have a large proportion of laborers who cannot get to a hospital quickly, and who cannot hold the quinine given by oral administration. Field staffs must be trained to give quinine intramuscularly. I think Dr. Macphail's percentage of quinine abscesses is remarkably small. My experience, with the best precautions, has revealed more than .5% abscesses.

Dr. B. M. Phelps. — I think the subject has been very well covered. There is one special point, however, that I should like to mention, and that is the reason why we give quinine intramuscularly and intravenously, now, in some cases of the benign tertian variety. We have very few malignant tertian cases. It is really necessary for us to use quinine intramuscularly for children coming into the hospital who are too ill to take it by mouth; and it is difficult to give quinine intravenously to small babies.

If a child or an adult comes into the hospital vomiting badly, and cannot take quinine by mouth, we give it intramuscularly. There is an economic reason for that, also. In most cases in which we find the blood positive for malaria, we treat them until their temperature is normal, and hold them in the hospital for six days after the fever has gone. The best thing to do is to treat them for three or four days, and then, provided the temperature drops to normal, keep them another six days.

In regard to giving quinine intravenously, I never found any reason for diluting it. We give 15 grains to a dose, very slowly, with a small-calibre needle. The reaction is at times rather startling, but generally brief, and we have experienced no fatalities. I have not been very successful in giving quinine intramuscularly

without producing abscesses. During some years in Honduras, a considerable number of the patients given quinine intramuscularly had abscesses, — and I gave a series of 100, myself, with careful attention to asepsis, applying tincture of iodine to the buttock and injecting deep into the ischio-rectal fossa. Of these cases, only 1% developed abscesses, a showing which I thought was very good. The percentage was higher than that, as a rule, in our hospital.

In closing, I wish to state that I consider that intravenous injections of quinine have a certain element of danger, and should be used only in those cases in which it is impossible to give relief by other methods.

Dr. W. E. Deeks. — Referring to my early experience, in the Canal Zone, in the treatment of malaria — we found that many of the quinine capsules and pills furnished us were insoluble and passed through the intestinal canal unchanged. Because of this we adopted the use of solutions of quinine in our routine treatment, and this method of using quinine has persisted up to the present time. It is very gratifying, therefore, to learn that quinine administered in capsule, friable tablets and friable pill form is as effective as the quinine solutions. This, of course, will do away with many of the objections raised by those who have been taking the liquid preparations; but as a great many patients cannot swallow pills, tablets or capsules, undoubtedly the liquid preparations of quinine will still hold a place in our therapeutic armamentarium.

In regard to the development of tissue necroses and abscesses, following the intramuscular use of quinine, it has been my experience that these are more likely to occur with hemoglobinuria, or in those suffering from extreme anemia or malnutrition. These untoward results, however, may be largely prevented by thoroughly massaging the area over which the injection is given, and then applying a hot-water bottle, which favors absorption. For this purpose, it has been my experience that hot applications are better than ice packs, and, furthermore are more comfortable for the patient.

The use of quinine hypodermically in subcutaneous tissue was almost invariably followed by necrosis of tissue, but if the quinine was injected deep—subcutaneously, no such untoward result followed. I used this method over an extended period, selecting the space behind the pectoralis major muscle or areas over the abdomen, injecting the solution down to, but not into, the muscles. This injection was followed by massage and hot applications, and the results were uniformly favorable. No matter where quinine is given hypodermically, it must not be repeated in the same area,

nor within six inches of the original puncture, until the tissues have had time to completely recover from the first injection.

Dr. Macphail's results in his hospital are exceedingly gratifying, and I know of no experiences which surpass his in the results obtained.

On the whole, I agree with Dr. Bass that in the majority of cases the routine method which he advocates for the treatment of malaria is perfectly satisfactory, but in tropical countries where we have so much pernicious malaria we must resort to intramuscular or intravenous injections in order to save the lives of our patients.

Dr. N. P. Macphail (Closing the Discussion of His Paper.) — I have listened with interest to the discussion on the administration of quinine in acute malaria, and I believe that we are nearly all in accord as to the relative values of the various methods of administration. I agree with Dr. Bass, that the great majority of all cases of malaria are controlled by the oral administration of quinine, and that there is no evidence to the effect that the more soluble salts give better results than the sulphate. I entirely disagree with him, however, when he says that a large percentage of the cases to whom intramuscular injections are given, develop abscesses, and I believe that the only possible reason for such result, is that the injection has been given carelessly.

In seventeen years of active work in a highly malarial district, I have given many thousands of intramuscular injections, and I must emphasize the fact that I have seen nothing worse resulting than an occasional necrotic process, with resulting abscess. This is a very small matter when compared with the large number of lives that have been saved by this method of getting quinine into the circulation of serious cases of malaria.

Dr. Bass has told us that his experience with quinine given by this method is limited, and I feel sure that when he has seen the type of malaria with which occasionally we have to deal in the Motagua valley, he will be inclined to agree with the views of those of us who have had to find ways of saving the lives of serious cases of malignant malaria.

I make no comparison between the value of the oral administration and that of the intramuscular method, as the types of cases in which each is used, differ entirely. And I have already stated that the great majority of all our cases are treated by the mouth. When, however, we get comatose cases, as well as cases in which persistent vomiting makes it entirely impossible to give quinine by the mouth, we are faced by the imperative necessity of still getting quinine into the circulation somehow.

Dr. Bass stated that his experience led him to the conclusion

that quinine given hypodermically or intramuscularly had little or no place in the treatment of malaria, and this statement leads me to the conclusion that he and I have practiced our profession among quite different types of malarial cases. In many serious pernicious cases, our only hope of saving life is the use of the needle. I must also emphasize that while quinine given intravenously does not seem to seriously affect a patient in robust condition, my experience leads me to believe that an intravenous injection of quinine in the case of a seriously ill patient, is, as said by Dr. Nutter, "very strong medicine." It is not a proceeding to be undertaken lightly in cases when the patient already has a low blood pressure, as is the rule in serious cases of malaria. And, while the quinine undoubtedly gets in contact with the parasites more quickly when given by this method, I seriously question whether it is a preferable routine measure in comatose or other serious forms of pernicious malaria.

There are extreme cases, however, when, in my opinion, an intravenous injection of not more than 7½ grains well diluted, should be given when the patient is first seen in a hospital where a trained physician is at hand. If any physician doubts the absorption of quinine when given intramuscularly, I advise him, as Dr. Bass did, to take an injection himself. I can, from personal experience, feelingly assure him that within twenty minutes after an injection of 22½ grains, he will be perfectly certain that the greater portion of the quinine is circulating.

In our hospital we have anywhere from 30 to 70 malarial patients all the time, and to give each one two intramuscular injections daily would be a great deal of work for the hospital staff. It takes a minimum of fifteen minutes of a trained nurse's time, to give an intramuscular injection of quinine and the necessary massage; so, manifestly, from an economic standpoint alone, we could not afford to make this procedure a routine measure. It is, however, an extremely valuable means of getting quinine into the circulation of the patient who needs it.

I am glad to note that a physician with the experience of Dr. Agramonte agrees with me on all points brought out in my short paper, and am especially glad that he has found the intramuscular method of introducing quinine valuable in his comatose cases and in other forms of pernicious malaria. His emphasis on the necessity for thorough massage of the parts, following injection, agrees exactly with what I have learned from experience.

I have also listened with pleasure to the discussion of Dr. Stephens, Dr. Connor, and Dr. Cran, and I note that their experience, practically all gained in districts where pernicious malaria is

common, has led them to the belief that the intramuscular method of quinine administration is a valuable one.

Sir Leonard Rogers has had a happier experience in giving quinine intravenously than has been my lot, and while we use this method when it appears justifiable or necessary, I must admit that we pay the procedure a great amount of respect in the case of very ill people, who are the only ones in whose treatment there is any excuse for using this method.

I am very glad that a physician of Professor Fülleborn's experience teaches that the intramuscular method has a valuable place in the treatment of heavy infections of malaria. During the time which he spent with me in Quirigua, two years ago, I remember with pleasure his approval of our method of treating pernicious types of this disease.

Dr. Castellani's discussion of my paper has been gratifying, and his description of the principal objections to the intramuscular method brought forward in the East, is interesting. The disinfection of the skin with Tincture of Iodine, and avoidance of giving two injections in the same spot, as described by him, are our routine, and are undoubtedly important factors in the avoidance of trouble. I have never known of tetanus being conveyed to a patient in this way, and I believe that thorough boiling of needles and syringes, and thorough preparation of the skin, should be sufficient precaution against such serious accident.

Dr. James's experience with parties going into the bush, is in line with mine in districts far removed from a hospital, where we have to depend on trained dispensers to give first aid. There, in my belief, the intramuscular method is seen at its best. A camp miles away in the bush is not the place to give intravenous quinine, even if a competent doctor were the first to see the patient, which happens rarely. A dispenser gives the patient, probably unconscious, an intramuscular injection immediately, and that is getting in its work while he is being brought to the hospital, a proceeding that may take many hours, and, in many instances, from unavoidable causes, may not be possible till the next day. Under such circumstances, even if necrosis and abscess do result, the time lost in curing the abscess is nothing, when compared with the probability that he would have died unless treated hypodermically.

Dr. Phelps and Dr. Deeks have made no particular criticism of my paper. I am glad that Dr. Deeks drew attention to the value of hot-water bottles applied to the site of injection, as an aid to absorption. I neglected to mention it, but we found that hot applications seem to help, and we often use them after the massage.

I regret that we have had so little discussion, with an account of

your individual experiences, on the question of liquid administration, as compared with dry preparations. Patients get very tired of the taste of liquid quinine, which we must admit to be very persistent, and if the excellent friable tablets that are on the market at present are proved to be as constant in their results as the liquid preparations, we shall have a certain percentage of our patients made happier in their misery while taking quinine over a lengthy period.

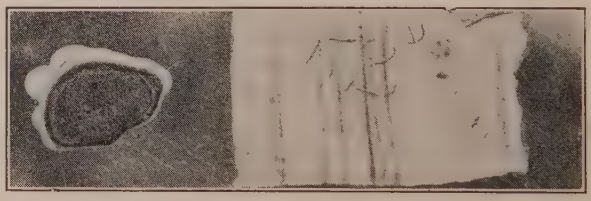
SOME MODIFICATIONS OF THE THICK FILM METHOD IN THE EXAMINATION OF BLOOD FROM MALARIA PARASITES

M. A. Barber, M. D. and W. H. W. Komp

The staining of thick films without the use of alcohol or acid in fixation, or dehaemoglobinization, is a text-book method familiar to you all. In our procedure we follow essentially this method, and our modifications are merely such as aim to improve the quality of the preparations and to simplify the mechanical handling of the slides.

I. The Use of the Modifications in Malaria Surveys

A thick and a thin film are made on the same 3″ x 1″ slide. We usually take the blood from a finger-prick; but we first carefully clean the finger with alcohol and gauze, since it is essential that no dirt be included in the thick film.

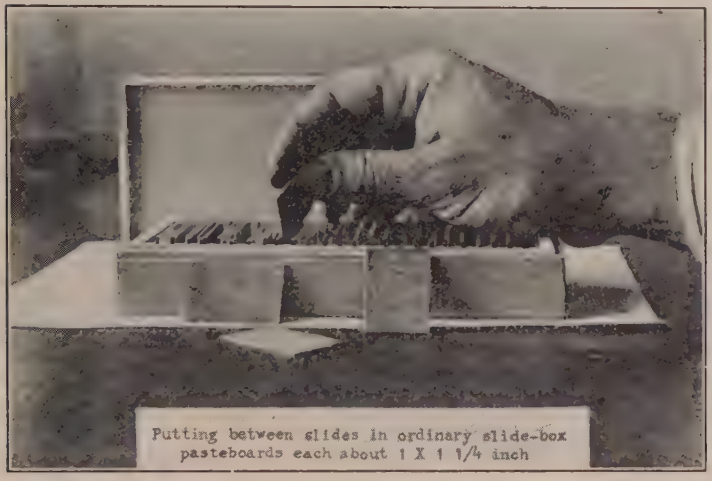


Thick Drop about ¼ C.C. Blood — Ordinary Thin Smear

As a slide is taken, a number, corresponding to a note-book number, is written with a lead pencil in the thin film. Labeled slides are placed serially in an ordinary slide-box, blood-side up, and the boxes are kept on end until the blood is dried. In order that dust may be excluded, the boxes are closed as soon as a group of samples has been taken. Boxes may be placed end up in a hand-bag and carried from school to school, or from village to village, until a survey is complete. The preparations may be stained as soon as the blood is well dried.

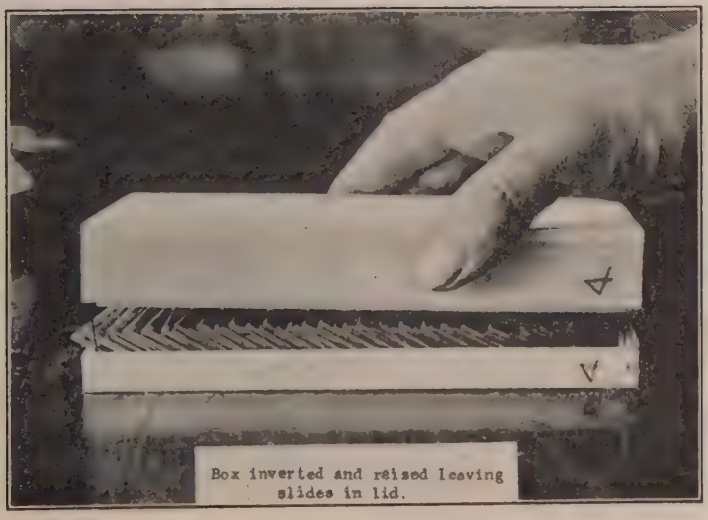
Staining

Before the slides are removed from the box, pieces of pasteboard — each about 1″ x 1½″ x 1/20″ thick — are

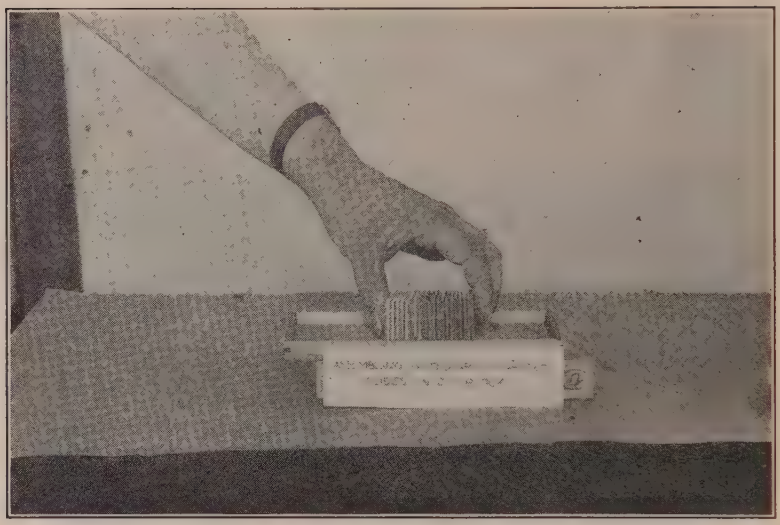


Putting between slides in ordinary slide-box pasteboards each about 1 X 1 1/4 inch

dropped between the thin smears of the slides, one to each interval. The lid is replaced and the box inverted.

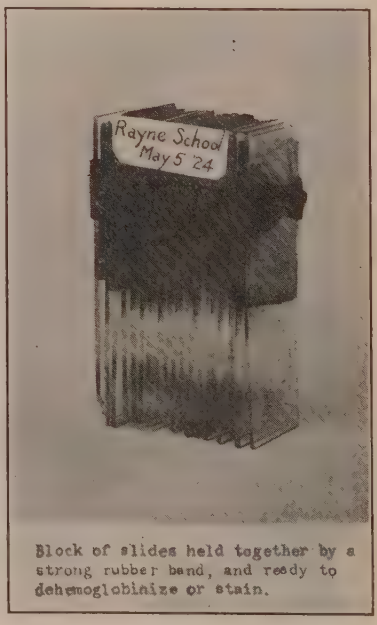


Box inverted and raised leaving slides in lid.



All the slides in a box, or any group of them, may now be easily assembled, fastened together by means of a stout rubber band, and given a group label.

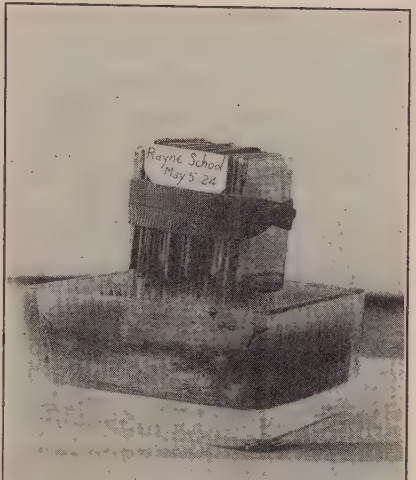
The block of slides is now stood in a vessel filled with clean water to a depth sufficient to well cover the thick film, without wetting the pasteboards or the thin smears. Dehaemoglobinization is usually complete within a few minutes. The block is now rinsed in fresh water, and placed, still wet, in a Giemsa stain.



Block of slides held together by a strong rubber band, and ready to dehemoglobinize or stain.

In making up the Giemsa, about 1¼ c.c. of stock stain is added to approximately 75 c.c. of water. This gives sufficient stain for a group of

25 slides. The stain is put into any vessel of such a size that the stain is of sufficient depth to cover the thick film without wetting the thin films. The block is stained for about ¾ hour. It is well to move it once or twice during the staining, in order to insure the distribution of the stain between the slides. If decolorization is indicated, the block may be placed for a few minutes in clean water, after staining. It is then placed on edge to dry. During the entire staining process and subsequently during storage, a group is kept together and the rubber band need be removed only when the slides are to be examined microscopically. They may then be put into a shallow box and removed in the same order as that in which they are recorded in the notebook.



BLOCK BEING DEHEMOGLOBINIZED OR STAINED AFTER STAINING, BLOCK IS RINSED (OR IF NECESSARY DECOLORIZED) IN WATER AND TILTED TO DRY.

Certain details may be briefly elaborated. Two prime essentials in the preparation of thick films are:

1. Avoidance of dust or finger dirt. To clean the finger or ear well requires but little time, perhaps four or five extra minutes for a group of 25 or 30 persons. The blood drop should be spread by dragging it about on the slide, not by rubbing the finger in it. Varying thickness in the depth of the drop is an advantage. The amount of blood spread may vary, but it is well to have at least 1/5 c.c.

2. A good quality of Giemsa stain is also essential. We have come to the use of Gruebler's powders exclusively, and we make up the stock stain according to the usual text-book formula.

Other details are worthy of mention. All are familiar with the importance of using a proper water for diluting the stock Giemsa stain. Distilled water made very slightly

alkaline, freshly caught rain water, and the like, are recommended by the text books. Considerable latitude, however, is allowable with respect to the quality of this diluting water. Old rain water, unmodified, or corrected by the addition of a drop of 1% lithium carbonate to 50 c.c., has served us well, as have also certain spring and tap waters, especially a tap water impounded on a mountain side. Water should be free, of course, from an excess of salts, as well as from large numbers of bacteria or infusoria likely to adhere to the slide and confuse the examiner.

The amount and dilution of the stain, the time of staining, and the amount of decolorization may also vary considerably, much depending on the quality of the stain and the age of the preparations. A few preliminary trials will usually enable one to adopt a satisfactory procedure, and some defects in the staining of a block can be easily remedied. If the first slides of a group appear to be over-stained, the block can be quickly reassembled and decolorized further, even after the slides have been long dried. If a group is understained, the stain may be repeated. The aim is, of course, to get distinct and characteristic stains of both the chromatin and cytoplasm of the parasites, and to have a light purplish background on which the parasites will be clearly defined. Decolorization is not always necessary. Dehaemoglobinization previous to staining may be omitted, but it seems to give clearer preparations.

When well-cleaned slides are used, one usually has little trouble through failure of the thick film to adhere to the slide. We require the slide-cleaner to wipe the cleaned and dried slides with an alcohol-moistened cloth, to insure as clean a surface as possible. A few hours' drying of the blood will make the films adhere better. If the drying is continued too long, especially in very warm weather, one does not get so nearly perfect a dehaemoglobinization or staining. In midsummer, we try to stain the slides the day they are taken. In cooler weather, two or three days may be allowed to elapse, without damage. The staining technique is so simple that it may be done on boat or train during the return journey from a survey.

In the description thus far given, no mention has been made of the use of the thin film. When the detection of malaria parasites alone is desired, as is the case in most

malarial surveys, the examination of the thin film is so rarely required that we have found it a waste of time and material to stain the thin films of all the slides. In case the thick film does not give the information desired, one has the thin film at hand and may stain it by Wright's, Leishman's, or any of the other commonly used thin-film methods.

II. The Use of the Thick Film in More Rapid Staining

In case it is desired to get an early report on a single slide or a small number of preparations, a staining of five or ten minutes usually gives a good thick-film stain, — always assuming that one has a good quality of Giemsa. At least five c.c. of stain should be allowed to each slide, and at least one drop of stock stain per c.c. of water. A freshly dried film may be dehaemoglobinized in two or three minutes using water alone, or the dehaemoglobinizing may be omitted. It is well to spread the drop more thinly for the rapid stain, else one sometimes has to rely on the examination of the edges of the drop. A thin film may be done on the same or on a separate slide. The examination of the thick film, when thus quickly stained, often saves much time and labor in case parasites are few.

We have used the thick-film method of making malaria surveys, for many years, and find it a helpful and time-saving method. We do not agree with James (James, S. P., *Malaria at Home and Abroad*) — that this method is unsuited for field surveys. A reliable assistant can be quickly taught to take the smears properly, and very simple precautions will suffice to insure clean preparations. Nor do we agree with James as to the necessity of confirming the findings in the thick films by examination of the thin. Crescents, plasmodia, and rings are often as well-defined in the thick film as in the thin, and vastly more of them can be found in a given time for comparison. The characteristic colors of chromatin and cytoplasm are sometimes more distinctly shown than in thin preparations. Errors in the interpretation of microscopic bodies may occur, of course, in any sort of preparation; but we believe that a clean, properly stained thick film contains no more pitfalls than the average thin film, at all events for an observer who conscientiously follows the golden rule: Regard as negative all doubtful cases.

One of the chief advantages of the thick film is the saving

of time in examination. In this connection, it might be asked how much time one ought to devote to a slide before finally calling it negative. This is a matter that must vary greatly with the examiner; it is difficult to standardize skill, experience and, above all, conscientiousness. It is helpful, however, for each observer to determine approximately how much error would result, in his own case, from a reduction in the time of examination. One of us recently had occasion to examine 65 thick-film preparations. The time required to find the first parasite was noted in each positive. In nearly every case, ten minutes were devoted to a slide before it was finally reckoned negative. Of the 65 examined, 29, or 44.6% were found positive. The results of the test showed that if only five minutes had been allowed in the case of those presumably negative, almost exactly the same positive percentage would have been obtained; if only three minutes, 27 would have been found positive — about 3% less than were actually found — an error of no great magnitude. In another series, some 500 cases were examined by the same observer, and about 35% found positive. Five minutes were devoted to the negatives. If only three minutes had been spent on them, the positive percentage would have been only 2% or 3% less. As a routine, we give a five-minute examination to a thick film before calling it negative. It is probable that in our own case it would be profitable to lessen rather than to increase this time. The error incurred through lessening would be small; and this error would be partly offset by the fact that additional slides could be examined during the time saved, and thus the error from random selection could be reduced.

Any survey can give only approximate results; and minor variations in positive percentages may possess but little significance. In particular instances (the diagnosis of suspected malaria in a patient, for example) the time of search may be lengthened. In any case, the finding of bodies suggesting chromatin granules, pigment, or even anemia, may lead one to prolong the search. Where one is merely looking for a gametocyte-carrier suitable for testing the infectibility of Anopheles, a few seconds' examination of the thick film often suffices. Above all, it is to be kept in mind that saving of

time, as well as accuracy, is attained by the use of clear, properly stained preparations.

DISCUSSION

Dr. Herbert C. Clark (*Opening the Discussion*). — During the months of April, May, and June we have been using two methods at Tela for the examination of malaria suspects: the Barber thick-film and the ordinary thin-film. Giemsa stain was used with the former, and Wright's stain with the latter. The technician has prepared and examined the thin films, while I have taken personal charge of the thick films. We have now examined 1,431 blood films by the two methods, and all these examinations were made on hospital admissions and dispensary visitors.

The Barber thick-film gave 45.8% positive results, and the ordinary film gave 17.5%.

Three hundred and fifty of these examinations were positive to the thick-film method, and negative to the thin-film.

Thirty of the examinations were positive to the thin-film, and negative to the thick-film method.

My short experience indicates that the Barber thick-film is splendid for those parasites old enough to contain an appreciable amount of pigment, but poor for the young trophozoites or ring forms. It is especially good for camp and village survey-work, and for detecting many of the "carriers." Frequently it affords an earlier diagnosis in our foreign population, who are prone to present symptoms with a very moderate infection apparent in peripheral blood films — an infection that would hardly be noted in the relatively immune native and negro.

A knowledge of the "carrier state" helps the surgeon avoid many post-operative surprises due to a latent malaria's becoming an active disease. The thick film also offers a relatively good idea of leucocytosis, eosinophilia, and pigmented lymphocytes. It is a particularly good method for dispensary practice, since many patients make but one visit to a dispensary, and it is therefore necessary to arrive at a diagnosis during this one visit.

Some of the advantages of the thick film, as I have used it, are the following:

1. It reveals the adults even when only a sparse infection is present.
2. It helps identify the type, in cases where perhaps only one or two young trophozoites are found in a thin film, by affording an opportunity to see some of the adult forms.
3. It furnishes a much more accurate idea of the incidence of malaria.

Some of the disadvantages are these:

1. Young trophozoites are difficult to stain because they contain little, if any, pigment. In a few cases where this stage was fairly numerous, the thick film failed to reveal the parasites.
2. The thick films are easier to lose off the slide than the dried and fixed thin film.
3. Anemic blood is difficult to prepare in thick film, and easy to lose in the water jars.
4. It is difficult—much of the time, impossible—to differentiate Tertian parasites from Quartan parasites.
5. A positive thick-film report given a medical officer in charge of natives and negroes, sometimes misleads the clinician and prevents, or delays, the recognition of the primary disease that brings the patient to the hospital. A doctor new to the Tropics is apt to find difficulty, for a while, in differentiating an acute malaria from a chronic or latent case.

I am pleased to keep in use both methods of examination, but if I were forced to use only one method, I would continue the use of the Wright's stained thin-film method for hospital and dispensary work, and the thick-film method for camp and village surveys. The thick-film requires more experience in its examination than does the thin-film picture with its good background of the red cells.

Dr. R. W. Hegner. — I am very glad to be able to recommend the thick-film method as described in Dr. Barber's paper, and as recorded by Dr. Clark. During the month preceding this Conference, I worked in Dr. Clark's laboratory in the United Fruit Company hospital in Tela, and saw all of the cases of malaria that came into the hospital during that period. This thick-film method, as used by Dr. Clark, is excellent for the older parasites — those that contain pigment, as Dr. Clark has reported. It fails, however, I think, in routine work to bring out the ring forms of the parasites — forms in which pigment has not yet appeared. I think that, while this method is uncertain at the present time, it can be modified and standardized in such a way that it will serve as well to bring out the young parasites as the older ones, and I recommend its use for routine work.

Dr. J. W. W. Stephens. — We use two kinds of thick-film method; in the first we do not decolorize at all; and in the second we decolorize, not with water, but with acetic alcohol, the preparations being much clearer than those with which water is used. I have employed this latter method for many years, with good results.

Dr. William M. James. — I have only to say that I agree with Dr. Hegner's suggestion that the thick-film method might be

modified, if it does not show the rings. The method we used was to decolorize in acetic alcohol, as suggested by Dr. Stephens, or with a weak acid alcohol. If you decolorize by means of either of these alcohols, you have to alkalinize the films (as the rings will not take the stain unless this is done) and then stain with any of the Romanowsky stains — as, for example, Leishman's or Wright's. This method is very good for hospital work, in doubtful cases, because it shows the young rings well. But whether in field work it would be worth the time involved, I am not prepared to state, and whether it would be practicable in survey work I do not know.

Dr. Foster M. Johns. — In anticipation of the large number of blood examinations to be required in the extensive anti-malaria carrier campaign — launched in 1917 by the International Health Board under the direction of Dr. Bass — I undertook an investigation into the proper methods of thick-film preparation, fixation, and staining. The results may be of interest to you. In the absence of Dr. Barber I cannot enter into a discussion of the relative merits of our methods, but I will describe briefly our technic, which has not been published, but which has given complete satisfaction up to the present time in actual field work, under many and varied conditions, and with many different technicians: —

1. Directly transfer slightly less than a drop (m) of blood to one end of the slide.
2. With the corner of another slide, spread the blood out to cover with thick and thin areas an area about one-half inch in diameter.
   Make the usual thin smear, as close as possible to the thick film. The thin film rapidly dries, and is immediately available to be labeled by writing a serial number in it, preferably with pencil.
3. Do your fixation and decolorization with alcohol containing sufficient acetic acid to decolorize in from three to five minutes. The entire slide is treated.
4. Wash in tap water.
5. Stain for several minutes in 10% solution of polychrome methylene blue (as prepared for making Wright's stain).
6. Rinse and counterstain with ½ of 1% eosin (y.w.s.).
7. Dry and examine.

With this method the danger of occasional loss of film is eliminated, and the acid decolorization is not a drawback as regards the separate stains employed. The thin film is always available for study, the erythrocyte showing a definite outline.

The methylene blue, methylene azur, and eosin elements of the stain are under direct control. The best possible contrast, *i. e.*, a deep blue protoplasm of the parasites and light pink background of erythrocytes, can easily be maintained under all field conditions.

The staining solutions can be used repeatedly, and the actual expense of stains can be reduced to only a fraction of the cost of Giemsa when staining jars and multiple slide-holders are used.

Dr. F. Fülleborn. — For about fifteen years we have used in our Tropical School, in Hamburg, for all routine work, a very simple method of thick blood-films. This method was worked out in East Africa, during the fight against malaria and sleeping sickness. A big drop of blood, spread out a little on the slide by the needle, is allowed to become perfectly dry and then is stained, without any other preparations, with diluted Giemsa's solution (1 drop to 1 cc. of distilled water) for about twenty minutes. Not only the pigmented forms, but also the smallest malaria rings, are quite clearly stained. Nurses can be trained in a few weeks to use this simple method.

Dr. Charles C. Bass (Closing the Discussion). — I think that when the lantern slides that go with the paper are shown, you will be still more impressed with the simplicity of the ingenious method which Dr. Barber has presented.

United Fruit Company Hospital at Port Limon, Costa Rica

BLACKWATER FEVER

J. W. W. Stephens, M.D.

When I considered what I should write on the subject of blackwater fever, I thought it would be best to avoid discussing the pros and cons of the very numerous views that have been expressed from the time of Tomaselli, and even earlier, up to the present day, and to limit myself to an attempt to put before you the facts of the matter, so far as I have been able to compile them amid the interruptions which seem to be the normal state of existence for the ordinary laboratory worker. I must apologize, then, for what I am going to do in cold blood — if I may use a most inappropriate expression in Kingston, Jamaica — for laying before you a dull recital of unconnected data.

Definition. — We may hardly define *blackwater fever* as a *fever* when, in certain cases, the temperature rises only to 100° F., or less, and when in others the temperature is said not to rise at all. We may hardly define it as a haemoglobinuria, since even this one of the most striking signs sometimes fails us. There are cases on record where the other symptoms and signs have been typical, yet in the urine there was no haemoglobin but bile pigment.

In animals the blood-destruction that follows the injection of a haemolytic serum is accompanied, as a rule, by the appearance of haemoglobin in the urine, but exceptionally the haemoglobin is replaced by bile pigment. Further, cases of blackwater fever are on record in which patients apparently suffering from a typical blackwater attack (temperature, vomiting, jaundice, anaemia) have, on examination, shown no haemoglobin in the urine, which was of a clear or turbid brown or porter color, owing to a pigment of unknown nature.

Haemoglobinuria is not necessarily an accompaniment of severe blood-destruction; *e.g.*, the drug toluene diamine in rabbits produces great blood-destruction, but no haemogloburia, while in the case of cats the haemoglobinuria is intense.

There are two processes involved:

1. Blood *destruction*, followed by cellular phagocytosis unaccompanied by haemoglobinuria; and
2. Blood *solution*, which implies haemoglobinaemia and haemoglobinuria.

While, then, we can hardly define blackwater fever, yet we have no difficulty in recognizing a moderately severe case. The rigor, the temperature, the jaundice, the vomiting, the distress, the rapidly progressive anaemia, the black water — these can hardly be confused with any other condition. But it would be a mistake to regard this as a picture of blackwater fever, for, wherever seen — whether in Macedonia, or in the tea-gardens of Assam, or, I think, in Panama — there are also such mild cases that there is no rigor, a slight shiver hardly noticed, and the patient is with difficulty persuaded to enter hospital, although he has passed black water. There are on record cases of this kind in which the patient was walking about, unaware that when he urinated he was passing black water. These mild cases may conveniently be termed "ambulant."

In this connection may be mentioned the problem of the recognition and definition of the conditions, if such exist, that have been termed latent blackwater by Blacklock, and pre-blackwater by Thomson.

Generalities. — I will briefly touch on some generalities, the bearing of which on the blackwater fever question I must leave, however, out of consideration here.

1. Black water may occur in a European arriving for the first time in the Tropics, as early as six weeks after his arrival.

2. It may occur as late as a year after he has left the Tropics.

3. Second attacks (or more than two) occurred, according to Deeks and James, in about 5% of the cases in Panama. The figure for Nigeria is about 20%.

4. Occurrence of ten or more attacks, in one patient, in the Tropics, is not very uncommon. Thirteen is the largest number I have found recorded, and these occurred in France, during the course of a year, in a patient who had returned from Senegal, West Africa.

5. Recurrences while the patient is in the hospital, are a peculiar and puzzling phenomenon. About 10%, perhaps, expresses the frequency. The interval between the first

attack and the recurrence may be as long as 12 days; or often, where the recurrences are numerous, only a few hours. Eleven is the greatest number of recurrences I have found recorded, the total duration of the attacks being 643½ hours.

6. Post-haemoglobinuric fever. An obscure condition, apparently not uncommon, of a fever, sometimes severe, lasting many days after the haemoglobinuria ceases. I have no figure for the frequency.

The Malaria Factor

Blood Examination. — Whatever may be the relation of blackwater fever to malaria, I believe the following facts are approximately correct:

Malaria parasites are found:

On the day before the onset, in about 75% of the cases.
On the day of onset, in about 50% of the cases.
On the day after onset, in about 20% of the cases.

Spleen puncture. — The evidence is conflicting — while Barratt and Yorke* in 6 cases found 0 positive, Christophers and Bentley in 5 cases found 4 positive.

Post-mortem. — In the literature, I find records of only 39 cases in which definite statements are made: pigment or parasites present in 32, *i. e.*, 82%.

Deeks and James state that Darling, at Ancon, has not failed to find evidence of malaria parasites or pigment in each case that came to autopsy.

Species of Parasite. — Malignant tertian parasites occur in blackwater in a proportion comparable to that found in the malaria cases in the blackwater area. Thus, Deeks and James in Panama found:

	P. falciparum	*P. vivax*
In malaria....	74%	26%
In blackwater.	76%	24%

i.e., practical identity.

Quartan Parasite. — I have found only 7 records of quartan in the whole of the literature. One of these cases, a very typical blackwater case, occurred in Germany in a patient who had never been south of Latitude 47° N.

*Note: Spleen puncture in 2 cases of "malaria," 0 positive.

THE QUININE FACTOR

That quinine can produce haemoglobinuria is certain. I will quote two cases only:

Koch records the following case:

1. 12th day in hospital. Quinine 1 gram — a few hours later, a moderate attack of blackwater; temperature, 104°.
   14th day. Quinine 1 gram — a more severe attack. As it was thought that blackwater might have to do with a fever recurring every second day, quinine was next given on:
   17th day. Quinine 1 gram — a few hours later blackwater; temperature, 99°.5.

Lovelace records the following case:

2. A Christian Scientist, in Brazil. Two previous attacks of chills and fever. At the third attack, at the entreaty of his friends, he took 5 grains of quinine. In a few hours haemoglobinuria supervened, and the next day he died.

It is impossible at present to say how far quinine has been responsible for precipitating the onset, in any particular case when quinine has been taken some hours before. Nor can we explain its mode of action. The administration of quinine to animals rendered anaemic by a haemolytic serum, has had no particular result. We are equally in the dark regarding the action of X-rays over the spleen, which is another of the several agencies which have the power of precipitating an attack.

THE BLOOD

Haemoglobinaemia. — (The normal value for haemoglobin in plasma is up to .25%, *i. e.*, equivalent to the colour given by .25 volumes of red cells in 100 of water.)

1. Dudgeon states that the evidence of haemoglobinaemia rapidly disappears. The observation should be made on plasma, and not on serum.

2. Christophers and Bentley found haemoglobinaemia in 33 of 33 cases.

3. Barratt and Yorke found haemoglobinaemia in 6 of 16 cases, values above .25%; the highest value being nearly 1%.

Methaemoglobinaemia has been observed.

Bilirubinaemia. — Normal value is 1 in 400,000. Dudgeon found bilirubin in 20 of 49 cases, *i. e.*, about 40%.

Urobilinaemia and Urobilinogenaemia. — No data exist.

The Urine

Oxyhaemoglobin. — Is the blood pigment usually present.

Methaemoglobin. — Found it in 8 of 10 cases (Barratt and Yorke). According to Christophers and Bentley, it is pronounced only when the urine has remained standing for some time.

Acid Haematin. — Arkwright and Lepper note that methaemoglobin may be mistaken for this.

Bilirubin. — Usually absent, but there are no systematic data.

Urobilin. — Sorensen, using a scale of dilutions, gives 10 as the figure for malaria, and from 25 upward for those liable to blackwater. There is general agreement that urobilin is increased in blackwater, and especially faecal urobilin, but the data are incomplete.

Brown or Porter-Coloured Urines. — To these I have already referred. The urine, at least, on admission, gives no haemoglobin bands, but is a light or dark brown; or a dark brown pigment may be present with the oxyhaemoglobin. Treatment of these brown urines with caustic soda gives haemochromogen (*i. e.*, reduced haematin).

Blood Destruction. — The haemoglobin that appears in the urine in an average case is equal to that derived from about 10 ounces of blood, *i.e.* about 5 ounces of red cells. But the *blood cells* may be reduced by 4/5 — if we assume that the blood volume has not proportionately increased.

For a person weighing 140 pounds, the blood volume is about:

$$\frac{140}{20} \times \frac{1}{10} \times 8 \times 20$$ ounces equals 112 ounces of blood and 4/5 of 56 equals 45 ounces, about;

that is, the red cell destruction is about 10 times greater than the amount of blackwater would lead us to suppose.

It appears as if the occurrence of blackwater had attracted to itself undue prominence, research having been directed largely to the study of the urine and the condition of the

kidneys; but perhaps the essence of blackwater lies elsewhere, *viz.*; in the study of the conditions surrounding this major blood-destruction. We may repeat here that in animals, at least, such destruction may occur without haemoglobinuria, the damaged corpuscles being engulfed by endothelial cells.

THE SEDIMENT

1. *Agglutinated red cells* in masses are described by Dudgeon in 4 of 43 cases, *i.e.*, about 10%.

2. *Haemoglobin casts* and granules form the main constituent of the sediment. The state in which the haemoglobin — if it be haemoglobin — exists, is not clear. By some, the granules are described as lying in a hyaline matrix. Similar granules can be demonstrated in the cells of the *tubuli contorti*. The granules dissolve in caustic soda and give the bands of haemochromogen. Plehn considers that these granules and casts are derived from the renal epithelium, and that the haemoglobin with which they are impregnated is derived from solution in the urine of blood that has escaped from the capillaries, into the tubules denuded of their epithelium.

3. *Renal epithelium* in casts, or otherwise, is also present.

4. *Red cells* are found in some cases; not in others.

PATHOLOGY

Spleen. — The distension of the sinuses with blood, the agglutination of red cells in the sinuses, and the active phagocytosis of red cells by the endothelial cells, constitute one of the most striking appearances. The Prussian-blue reaction for haemosiderin shows the presence of small or large granules *in* the cells, or a diffuse staining only.

Liver. — The sinuses are dilated, and here again autoagglutination of red cells is seen. The free-iron (Prussian-blue) reaction may be intense.

Kidneys. — Degeneration of the epithelium of the convoluted tubes is recorded by some observers as an almost instant appearance; by others, only in a few cases.

Haemosiderin occurs in the epithelium of the convoluted tubes. The haemoglobin casts and epithelial casts in the tubuli recti are interpreted by most observers as being respon-

sible for the suppression of urine, but as to the nature and origin of these casts there is still, as we have seen, uncertainty.

Speaking generally:

Dudgeon regards the free iron (Prussian-blue) reaction, *i.e.*, the presence of haemosiderin in the spleen, liver, and renal epithelium as the most characteristic appearance in the organs. It explains why the haemoglobin in the urine is not proportionate to the destruction of blood corpuscles. This Prussian-blue reaction is seen in chronic malaria. It occurs also when a haemolytic serum is injected into an animal. There is the same picture of the liver, spleen, and kidney cells filled with granules giving the Prussian-blue reaction.

It is worth pointing out that this deposit, in the tissues, of blood in the form of haemosiderin is no accidental process of no particular significance; on the contrary, it is purposeful. It is from this source of free iron that the body gets the iron necessary for the rapid building up of fresh corpuscles, that takes place when the blood cells have been destroyed by, for example, a haemolytic serum.

What finally is the essential cause of the blood-destruction in blackwater?

In paroxysmal haemoglobinuria, due to cold, a haemolysin can be shown to be present, by experiments *in vitro*, but all such attempts to demonstrate a haemolysin in malaria or blackwater have failed, or at least have given uncertain results. But it does not follow that such a haemolysin does not exist, for the simple reason that, once we inject a haemolysin into an animal, we can no longer detect that haemolysin except by its lethal results.

Besides paroxysmal haemoglobinuria, due to cold, there are haemoglobinurias that have no paroxysmal relation to cold, and in which, so far as I know, no haemolysin can be demonstrated. Haemoglobinuria sometimes occurs in pernicious anaemia, and here again I do not think the presence of a haemolysin has been shown. I think, then, that until the presence of a haemolysin can be negatived by good evidence, we may adopt this as a provisional hypothesis. It is not likely that we shall understand what it is that starts the

blackwater process until we can explain, also, what the mechanism is that produces the paroxysm in the haemoglobinurias to which I have referred. A point of great interest in blackwater is that it presents us with a problem of a different nature from those involved in the common tropical diseases.

You are familiar with the big assaults on the position, made by Barratt and Yorke, Deeks and James.

It is now nearly a quarter of a century since Christophers and I first studied blackwater fever in Africa and India.

I am watching with great pleasure the latest attack on the problem now being carried on by the keen, alert intelligence of my friend Dr. Thomson.

THE MORPHOLOGY OF *PLASMODIUM FALCIPARUM* FOUND ASSOCIATED WITH HAEMOGLOBINURIC FEVER IN SOUTHERN RHODESIA; WITH NOTES ON THE BLOOD CHANGES PRODUCED BY THIS PARASITE, AND ON THE PREVENTION OF BLACKWATER FEVER

JOHN GORDON THOMSON, M.A.

In the consideration of malaria as the primary causal factor necessary for the production of blackwater fever, too little attention has been directed to the species of parasite concerned. Haemoglobinuric fever occurs associated with each of the three recognized species, but, in my opinion, the only one concerned as the true causal factor is *P. falciparum*. In countries where malaria is intense, and where at certain seasons benign tertian is common, mixed infections occur, and the finding of *P. vivax* associated with haemoglobinuric fever does not mean that this parasite caused the disease, but only that it acted as the excitant of the attack. Deeks and James (1911) drew attention to this important point in their excellent paper on haemoglobinuric fever, and showed that if the previous infections were taken into account, the percentage of malignant tertian was correspondingly raised. They found that 87.2% had been infected with that parasite. The valuable statistical evidence of Stephens (1913) demonstrates that pernicious malaria is most commonly associated with blackwater fever. He draws attention to the findings of Lovelace (1913) and is at a loss to explain the high percentage of benign tertian in his findings, but there can be no doubt that in this instance we are dealing with a district in which benign tertian was common and mixed infections occurred.

In the tropics of Africa malignant tertian certainly forms by far the greatest proportion of infections, and benign tertian is comparatively rare. In Southern Rhodesia, during 1923, of 100 positive blood films I found *P. falciparum* in 96.0%, *P. vivax* in 3%, and *P. malariae* in 1%. The previous year (1922) produced very similar figures. In 23 cases

of blackwater fever, before the onset I found *P. falciparum* (asexual forms) in every instance. From my investigations of the literature on this subject, and from my own researches in Rhodesia, I have formed the definite opinion that haemoglobinuric fever is caused only by repeated and intense infections with pernicious malaria, over a prolonged period, and that the presence of this parasite in a high percentage of infections in any given area is the most important factor necessary for the production of this condition.

Regarding the variety of blackwater fever in the Island of Ceylon, which seemed to be highly malarious, the percentage of malignant tertian in one part of that island is given by S. P. James and Gunasekara (1913) as only 10%; and Manson-Bahr (1913) in another area of the same island also found an extremely low percentage of infections with the same species. The scope of the present paper does not permit me to deal further with all the evidence available in support of the hypothesis that pernicious malaria alone is responsible for blackwater fever.

In all cases of blackwater examined before the onset, it could not be claimed that the infection in the peripheral blood was heavy. In malignant tertian malaria, however, an examination of a single blood-film gives no real indication as to the amount of infection in the body. The knowledge of this fact must have been lacking in the case of those who have brought forward the argument that the severity of the haemolysis can in no way be accounted for, owing to the scarcity of the parasites in the blood at the onset of symptoms. In all positive cases there was a remarkable absence of acute symptoms. The patients felt out of sorts, were anaemic, and had characteristic lemon-tinted sclerotics. The majority complained of biliousness, or previous attacks of it, and attacks of indigestion with occasional fever. All these symptoms were characteristic of that long-standing form of pernicious malaria, and, in all instances, up to a short period before the onset of haemoglobinuria, the patients were able to be out of bed. It was a routine practice to take a blood film from all patients — otherwise a malarial infection might have been missed entirely, owing to the fact that the patient did not complain of acute symptoms. In twenty-three of my cases, the parasites disappeared from the peri-

pheral blood the day after the onset of haemoglobinuria. Thus, it was obvious that it would have been impossible to diagnose these cases of malaria, if examined later with the microscope.

THE MORPHOLOGY OF THE PARASITE

Ever since the study of the malaria parasite was begun, it has been usual to regard only one species in benign tertian and quartan respectively, but difficulties have arisen with regard to the malignant tertian. These are due to the various clinical manifestations caused by it, and also to the enormous differences seen in the shape and size of the asexual forms in the peripheral blood. Grassi and Feletti described three species associated with pernicious malaria, viz.: *Haemamoeba praecox* (pigmented quotidian), *Haemamoeba immaculata* (non-pigmented quotidian), and *Laverania malariae* (the parasite associated with crescents). A study of the morphology, however, has not sufficiently shown that there are three species, and it has become generally accepted that there is only one, viz.: *Plasmodium falciparum* (syn. *Laverania malariae*).

If, then, we assume only one species, as indicated by the morphology, we must at the same time regard it as capable of producing clinical symptoms, of almost protean character, at different times in the same patient, and also in different patients. This is due to two factors: (1) varying virulence of the parasite, and (2) varying resistance of the infected individual. In a film from India, Stephens (1914) described "tenue" forms of the asexual parasite, which he named *P. tenue*, and Sinton (1922) described similar forms from the same area. Sinton's description is especially interesting, because he showed that the morphology varied according to the time the blood of the patient was examined. The youngest rings were 1.5μ to 2.5μ in diameter. In 10 to 12 hours they measured 2.5μ to 3μ, and later 3μ to 3.5μ, when malignant stippling appeared (Stephens and Christophers' or Maurer's dots). From the 26th to the 32nd hour after schizogony, "tenue" forms appeared in large numbers. It seems probable, from these observations, that "tenue" forms in malignant malaria may be much commoner in certain territories

than was previously supposed. I encountered them frequently in Southern Rhodesia.

Craig (1921) described two species of malignant tertian. He bases his differences on the sizes of the asexual rings, the schizonts, and the gametocytes. His description of *P. falciparum* is this: — asexual rings, 2μ–3μ in diameter, which increase in size in 18 hours to 3.5μ; the schizonts fill 2/3 to 3/4 of the red corpuscle, and there are from 10 to 30 (usually 18–24) merozoites. He defines a new sub-species, *P. falciparum quotidianum*, in which the youngest asexual rings measure only 0.5μ. Double and triple infections of corpuscles are common, and the schizont, when fully developed, fills 1/3 to 1/2 of the corpuscle, which is shrunken, crenated, and of a dark olive colour. In 24 hours the parasite gives rise to from 6 to 18 (but usually 12 to 14) merozoites 0.5μ in size. Further, the crescents are smaller, by at least 1/3, and are plumper than those of *P. falciparum*, being kidney or bean shaped, rather than crescentic.

These observations of Stephens, Sinton, and Craig are of great interest, and, although there is, in my opinion, insufficient evidence that *P. tenue* and *P. falciparum quotidianum* are true species and sub-species respectively, nevertheless these morphological variations may point to certain changes produced by immunity, environment, transmission, and so on.

In view of these data, I felt it would be useful to examine carefully the parasites as found associated with blackwater fever in Southern Rhodesia, to determine whether, in any respects, these differed from those commonly associated with ordinary malarial attacks. In comparing carefully the morphology of the parasites as they occurred in pernicious malaria and haemoglobinuric fever, I was quite unable to determine any definite morphological differences in Rhodesia.

Cultures, by Bass' method, of 18 cases, 2 of which afterward developed blackwater fever, were successfully obtained. In the human body, and also in cultures, as soon as the parasites lose their ring shape — and pigment collects — they clump in masses round the endothelial cells. I have illustrated this in a film placed under the microscope. They remain agglutinated until schizogony is complete, as

illustrated in another specimen. This clumping round the endothelial cells explains their arrest in the capillaries of the internal organs.

The fully grown schizonts fill, as a rule, about 2/3 of the corpuscle, but they may be larger or smaller, and the merozoites vary both in number and in size. The smallest may be only 0.5μ but they are usually 0.7μ in length, and may vary in number from 10 or less to a maximum of 32. The youngest rings in the peripheral blood measure about 1.5μ, and 2 dots of chromatin are common. As they become older, they increase in size to 2.5μ, 3μ, 3.5μ, and even 4μ in diameter. As the asexual parasite grows, some peculiar chemical reaction takes place in the corpuscles, which results in a darker staining reaction with Romanowsky stains. The red cell does not enlarge, and the dark staining reaction indicates the so-called "brassy" corpuscles described by many observers.

At this time the characteristic malignant stippling of the corpuscles appears. The asexual rings remain in the peripheral blood, and increase in dimensions for at least 24 hours or longer; it is for this reason that different observers have given different measurements to the ring. The size, as a matter of fact, depends upon the time the blood film is examined. Examinations of films at different periods show enormous variations in the shape and size, in any individual case. We find small typical rings with two dots of chromatin, accolé forms, large coarse rings with a large amount of cytoplasm, oval forms, tailed forms, band-shaped forms simulating quartan, piroplasma forms, and even "tenue" forms.

The gametocytes may be crescent shaped, or shorter and more bean-shaped. Although "tenue" forms were common at certain stages, I never found such large numbers of these as occurred in the films of Stephens and Sinton. Blood smears, from blackwater fever, taken just before the onset, commonly showed large rings measuring 2.5μ in diameter, or more, and if appropriately stained showed the altered staining reaction of the corpuscle and malignant stippling.

I consider that it is this altered chemical reaction of the red cells which is responsible for the production of blackwater fever by this parasite. We can regard these altered corpuscles as foreign bodies capable of producing a specific

haemolytic amboceptor, and this haemolytic substance will act only on cells so altered. In one blackwater fever case that I kept under observation for four days before the onset, these large rings with chemically altered corpuscles and pernicious stippling, occurred daily in the peripheral blood. A dose of quinine precipitated a sharp attack of haemoglobinuric fever. In two cases of quinine haemoglobinuria in children these altered cells were also constantly present. Unless a film is stained intensely and with appropriate stain, *e.g.*, a good brand of Leishman's stain, neither the dark colour of the infected corpuscle nor the pernicious stippling will be detected. When the asexual rings are very young, there is no alteration in the staining reaction of the containing red cells. Once the staining reaction of the corpuscle has changed, it remains so until schizogony is complete. This I was able to determine by cultural methods.

From these facts I concluded there was only one species of malignant tertian, in Rhodesia, responsible for malaria and blackwater, and that the different forms were morphological variations of it, *viz.*: — *Plasmodium falciparum.* Here is the most interesting question to me, "Is there a particular variety of *Plasmodium falciparum* that produces this chemical change in the corpuscles, and another that does not do so?"

My experience in staining films of *P. falciparum*, mostly from acute cases, in England and elsewhere, is that pernicious stippling and altered staining reaction of the corpuscles are seldom, if at all, well demonstrated. This may be due to one of two factors, *viz.*: — the age of the asexual rings at the time the film was taken, or the actual method and stain used. In Rhodesia I found that if I stained a film just after a paroxysm, young rings did not alter the corpuscle, but that if a film were taken later from the same patient, the rings having increased in size, it was possible to demonstrate both the altered staining reaction of the corpuscles, and pernicious stippling. I have placed under the microscope specimens from blackwater fever and malaria, showing this.

THE PREVENTION OF BLACKWATER FEVER

I have no intention of dealing fully with this subject in the present short paper, but in view of the importance of

this conference from a public health point of view, I should like to state that, as haemoglobinuric fever is undoubtedly due to repeated intense infection with *Plasmodium falciparum* — usually over a prolonged period of several months or years — we have at hand a disease that can be not only controlled, but absolutely abolished, by anti-malaria measures. Malignant tertian is very responsive to quinine treatment, much more so than benign, so it is certain that, if this drug were properly used in treatment and prophylaxis, by this means alone in areas where other methods of malarial control were imperfect, we could practically abolish the disease.

Recently it has been proved that quinine taken prophylactically, by the method usually adopted in tropical countries, is insufficient to prevent infection, but its regular use prevents the parasite from doing the same amount of damage, and so, in my opinion, prevents blackwater fever. Quinine has fallen into disrepute because it has been improperly used. I never saw a case of blackwater develop in a person who took regular daily doses of quinine prophylactically, even though he might develop malaria. But all the cases that I investigated in Rhodesia (more than 150) took intermittent occasional doses quite insufficient either as a cure or as a preventive; and when finally a dose was taken, and followed by blackwater fever, the drug was damned. There is, throughout the Tropics, a great need for proper instruction and effective propaganda to the laity, regarding the use of quinine.

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DISCUSSION

Dr. William M. James (Opening the Discussion). — One of the unfortunate features in gatherings of this kind is the lack of time for the discussion of such interesting subjects as are covered by the papers just read. Blackwater fever is a highly controversial subject, and there has always been a difference of opinion as to its aetiology and treatment.

I feel confident that, if Dr. Stephens were so inclined and would take advantage of a little more time, he would give us his opinions on the aetiology of blackwater fever, and I believe these opinions would be found to be correct. I recall the work of Dr. Stephens many years ago and that of his colleagues as pointing out the way to the solution of the problem of the aetiology of blackwater fever. I do not know whether Dr. Stephens has solved this in his own mind, but I believe that he has given more study to this subject in all of its aspects, and knows more about it, than any one else interested in tropical medicine.

When the clinician discusses the aetiology of this disease, or tries to get at the bottom of the perplexing problem of why, other factors being equal, blackwater fever occurs in some cases of malaria and not in others, he is confronted with a difficult task. As soon as he assembles his data, and states what he believes to be a triumphant solution, he finds the laboratory men entrenched behind a mass of facts, of whose very nature he is ignorant. I believe that the solution of this problem lies in the hands of the laboratory workers, and that it will eventually, be found there. The clinician, by a careful observation of the many factors which must be taken into consideration, and a careful reporting of those factors, can aid greatly in this direction.

But, as Dr. Stephens points out, we have to do here with factors in which a thorough knowledge of chemistry is of the highest importance, especially that chemistry which deals with the human body as a laboratory. I am not qualified to discuss this paper from such a viewpoint. My experience with blackwater fever is that of one who has seen this phenomenon under clinical conditions and at autopsies.

I believe that today there are few, if any, who hold that blackwater fever is a clinical entity unconnected with malaria.

When Dr. Deeks and I first took up our clinical studies, there were quite a few who did not believe in a reciprocal relationship between blackwater fever and malaria — that is, they did not believe that malaria was the essential predisposing factor.

However, as time went on, these objections began to disappear. Those who held them were forced to admit that if "blackwater"

is independent of malaria, then it must be due either to some hypothetical parasite, having exactly the same distribution as malignant malaria, or else to some other cause which occurs only in the same areas.

More careful investigation showed that *Plasmodium falciparum*, even when not found at the time of the attack, was associated with previous attacks of malaria in so high a percentage of cases of blackwater fever, that it could not be ignored as a factor. At autopsies we found, in the rare instances in which *Plasmodium vivax* was the only parasite in the peripheral blood, various stages of developing crescents in the spleen and the rib-marrow.

In the Canal Zone we were able to work under conditions which were not before to be obtained, and which will not in all probability be paralleled in the near future. There were three distinct races of men working under the same general conditions of sanitation, yet very widely separated in their methods of living.

There was a very large negro West Indian population, in which there was more or less immunity against the effects of malaria. This class lived in the sanitated districts of the Canal Zone, but no manner of persuasion could induce them to use the screened quarters provided for them. There were from 30,000 to 50,000 of them employed at one time or another. In addition, there were about 6,000 employees who were imported from countries in the Mediterranean littoral. About 5,000 of these came from all over Spain, the other 1,000 was made up of Italians, Greeks, and Turks. These last came from malarial countries, but most of the Spaniards came from districts in which there was little, if any, malaria. They lived in exactly the same localities as the Americans and the negroes; but, unlike the negroes and the Americans, they brought with them very few women and children. These Spaniards lived, for the most part, in the screened barracks provided for their housing. But they could not be induced to take advantage of the screening. They would prop open the doors and make holes in the screens, despite all efforts to prevent them. They would also frequent the native huts on the edges of the Canal Zone villages and at a little distance from them.

The American population averaged about 10,000 during the construction of the Canal — approximately 5,000 to 6,000 men, 3,000 to 4,000 women and children. This class lived in the screened quarters provided for them, and was very particular to see that the screens were properly cared for and kept free from holes. The American housewife of the construction days would complain at once if her screening was not properly looked after. The screening was held in high regard, because it kept out not only mosquitoes, but the numerous other flying insects as well. I

might remark here that it has been the custom of the American people, for many years prior to the construction of the Canal, to screen their houses during the summer months, especially in the country, as a protection against flies.

I believe that had we undertaken the construction of the Canal before the discovery of the mosquito as a means of transmitting malaria and yellow fever, we would have screened against it, if for no other reason than that of comfort.

The distribution of malaria, as determined by positive blood-findings, varied in inverse proportion to immunity and to screening. The negroes and the Americans showed approximately the same rate per 1,000. This was due to the relative racial immunity of the negro, as he was as much exposed to infection as the European. But the rate per 1,000 among the European laborer was from 5 to 10 times that of the Americans and of the negroes. And where Americans were exposed to infection — as in temporary camps of the surveying parties, and during the reconstruction of the Panama Railroad, in districts in which sanitation was not carried out — there was also a very high malaria rate among them.

Now, we found that the distribution of blackwater fever was in almost exact proportion to the incidence of malaria. That is, there was not a great deal of "blackwater" among the Americans or the negroes, but there was a very high rate that followed very closely the malaria rate, among the European laborers. Blackwater fever also followed the seasonal incidence of malaria in all classes. There is a dry season with very little rain, lasting about 4 months, from January to May, and the malaria rate fell sharply in correspondence, and rose again with the beginning of the rain. This incidence correspondence between "blackwater" and malaria was first pointed out by Dr. R. C. Connor, about a year and a half before Dr. Deeks and I published our monograph.

Another interesting factor with respect to immunity is, that blackwater fever very rarely occurs among the Panamanians of mixed blood. A few cases have been reported, but personally I have never seen one, although this class, outside of the cities of Panama and Colon, has been and still is heavily infected with malaria.

Local physicians, like Dr. Carlos Cooke and Dr. Uriola, who were with the French Company during the construction of the Canal, told us that this was true in those days as well. They saw a great number of cases of blackwater fever and malaria among white Panamanians and white aliens, but very little blackwater fever among the many negroes employed by the French Company, or among Panamanians of mixed blood.

The proportion of the parasites was remarkably constant, and still is. Many physicians, working under various conditions of examination of the blood, returned 80% of *Plasmodium falciparum*, 24% of *Plasmodium vivax*, and about 1% of *Plasmodium malaria*, over a period of many years. This same percentage was maintained in the blood-findings in cases of blackwater fever. But here another interesting factor enters. A very high percentage of the cases that had *Plasmodium vivax* in the peripheral blood at the time of the febrile attack which preceded or accompanied the "blackwater," could be shown from the hospital records to have had *Plasmodium falciparum* in the peripheral blood on previous admissions.

These are clinical factors which must be taken into consideration in the explanation of the aetiology of blackwater fever. It is fair to assume from them that blackwater fever occurs directly in proportion to the intensity and the distribution of *Plasmodium falciparum* infections. I am entirely in agreement with Dr. Thomson in his presentation of this statement. The mass of evidence is wholly in favor of it, and personally I am very doubtful as to cases of blackwater fever which are reported to have occurred in people who never had malaria.

With respect to the *treatment* of blackwater fever, I have very little to say. My own treatment of it is prayer. This is not because I do not regard proper symptomatic treatment as of great value. Our records show that there is no difference whatever with regard to the administration of quinine. Our cases were equally divided between those who received quinine, and those who did not, and the results were about the same. It is very seldom that a heavy malarial infection in the peripheral blood persists after the onset of "blackwater." The same condition is also found at autopsy. We have seen cases in which there was a very heavy infection in the peripheral blood at the time of the onset of "blackwater," but which died without quinine treatment within 24 hours. At autopsy, various developmental forms of crescents would be found, but no asexual forms. Most authorities agree, and it is certainly our own experience, that as a rule the corpuscles which contain parasites are the soonest destroyed by the mechanism that brings about the hemolysis. If this be true, then it makes but little difference in most cases whether or not quinine is given. It is only very rarely that a heavy infection will persist after the onset of the "blackwater." I have seen only one such case, and then it was a simple tertian infection.

The point has been made in the discussion of Dr. Thomson's paper as to whether there are more than one species included under

the name of *Plasmodium falciparum*. The reason for this belief is to be found in the various descriptions of the morphology of this parasite, and in the peculiar variations in the temperature curve. With respect to the parasites themselves, I agree entirely with Dr. Thomson that the numerous morphological variations in the younger forms of the species resolve themselves in the end into homogeneous organisms.

I once had the opportunity to test this in experimental work. I have not the time to go into the details and shall have to ask you to accept the conclusions. A considerable number of infections with malignant tertian parasites were observed for several days, without quinine administration. We were trying the effects of other remedies, and I may add here that none of them was of the slightest value. Whatever temporary improvement resulted, could be paralleled by control cases in which no medicine of any kind was given.

Most of these cases showed varieties of a tertian temperature. The difference between these curves, and those produced by the *Plasmodium vivax*, was that in the former the fever lasted from 24 to 36 hours, and had a plateau between the rise and the fall of the temperature. This is the well-known type which is called *subtertian*. These paroxysms frequently overlap, producing a continued fever very much like that seen in typhoid. On the other hand, the paroxysms were sometimes shortened, and a temperature curve indistinguishable from that of ordinary tertian was seen. Rarely a true quotidian rise and fall was observed.

The difference in these temperature curves, in my opinion, was due to a combination of immunity against the toxic effects of the parasites, and the amount of the infection. Just as in benign tertian infections one finds a double infection with a quotidian rise and fall of temperature, and sometimes overlapping, so one sees the same in malignant tertian infections. Also, it is a well-known fact that in primary infections the fever is longer in proportion to the cycle of the parasite than it is in those who have had repeated attacks of malaria.

In malignant-tertian infections one frequently finds repeated broods of parasites of the same age appearing in the blood at shorter intervals than 48 hours. If these broods appear every 24 hours, and there is a certain degree of immunity, one may find a quotidian fever. At autopsy in very severe and untreated infections, although only one stage of the parasite may appear in the peripheral blood, in smears from the spleen and the rib marrow all ages of the cycle may be found.

To one who is familiar with malaria, these facts will explain the

many variations of the temperature curves seen in infections with *Plasmodium falciparum*, without the necessity of assuming a multiplicity of species. It is quite true that there are morphological differences, at times, in the younger forms of the parasite, but these can be explained by variations due to the activity of the infecting species. The same is seen in other protozoa, notably in the entamoebas of the human intestinal tract.

I wish to take this occasion to congratulate Dr. Stephens and Dr. Thomson on their very interesting papers, which I am sure we will agree form most important contributions to the literature on malaria.

Dr. C. C. Bass. — My experience with blackwater fever has been very limited, and therefore I hesitate to offer any discussion whatever. I wish to express deep appreciation, however, of the very able presentation of these valuable papers. They lead us to feel that we are at least on the right road toward a solution of the problem of the cause of the disease. Even the very little experience that I have had, leads me to the same opinion that seems to prevail with the speakers who presented the papers: namely, that there exists a close relationship between haemoglobinuria and malaria.

I wish to remind you that, although Dr. James' remedy of prayer is perhaps the best treatment for the individual patient, the remedy for the disease in general is the prevention of malaria. Haemoglobinuria occurs chiefly in improperly treated cases of malaria of long duration. To cure such cases by proper treatment before haemoglobinuria develops, would prevent it and save more lives than any method of treatment after the disease begins.

Dr. Friedrich Fülleborn. — Although there was very much severe aestivo-autumnal malaria among the German troops in Macedonia during the Great War, there were only a very few cases of blackwater fever, — on the other hand, there were very many such cases among the Allied troops in Macedonia.

Dr. Aldo Castellani. — I really have not the qualifications to take part in this discussion because, although I have seen and treated a large number of blackwater fever cases, in many parts of the world, I have never carried out any scientific investigations on the subject. Dr. Thomson asked me what is the type of malaria parasite prevalent in Ceylon. Chalmers and I investigated the question some years ago, in both private and hospital patients, and our results were the following:

The commonest type was the benign tertian; the next, the malignant tertian; and the least common, the quartan. I must also add that, in Ceylon, blackwater fever is rare, but in my

opinion this fact does not in any way refute the theory that blackwater fever is in many cases a manifestation of malaria. The term blackwater fever covers probably three different conditions. In most instances — I should say, in 80 to 90% of the cases — the condition is a manifestation of malaria. In a few instances it may be quinine haemoglobinuria. Finally, I have the impression that when we have omitted all the cases due to malaria, there is a residuum (say 2 or 3% of the cases) the clinical features of which give the impression that we are dealing with a specific disease in a class of its own.

I have seen blackwater fever in Ceylon, though it is rare, and have seen cases in the Balkanic war zone, and in the south of Italy. In those regions the condition is always a manifestation of malaria. In Uganda, while the great majority of cases are of malarial origin, on several occasions I saw a type of blackwater fever that seemed to be somewhat different. However, as a general rule, blackwater fever is malaria, as clearly shown by Deeks and James, Stephens and Thomson, and I often give quinine in the following way: an intramuscular injection of quinine (5 to 10 grains) twice daily, and, in conjunction with it, 5 grains of calcium lactate by the mouth, hourly, or 10 grains every 3 hours.

Dr. R. R. Nutter. — We do not have a great deal of blackwater fever in Honduras. I was with Lovelace in the Madeira Valley, in Brazil, when he reported the 500 cases referred to by Dr. Thomson. Our records were by no means exhausted, to secure that number of cases for the report.

Those of the staff who had been in the Panama Service were astonished at the prevalence of blackwater fever on the Madeira-Mamore, and I am forced to believe that prophylactic administration of quinine played an important rôle in relation to its incidence and character. The type was milder than what we saw in Panama, and there was a lower mortality rate. Many of the patients entered the hospital with a history of several previous attacks, from which they had recovered without medical attention. These patients were mostly Spaniards working on grading contracts, remote from the hospital.

In the construction of the Madeira-Mamore Railway 6,000 laborers were employed, about one-half of whom were South Europeans. They were very much under control, and were compelled to take 10 grains of Quinine hydrochloride in capsules, daily. Such general administration of quinine, which was insufficient to cure this malaria, I believe to have been partly responsible for the prevalence of blackwater fever. On the other hand, I am convinced that the malaria mortality was reduced by the prophylactic quinine. Cerebral types were relatively infrequent.

Dr. Roland C. Connor. — Dr. James has so thoroughly covered the subject, including our experience in the Canal Zone that there is not much left to say. I was in charge of the white foreign section during the time we had most of our blackwater fever. In 1909, I read a paper before the Canal Zone Medical Association, which covered my experience in the treatment of those patients, and gave the statistics that we had available regarding them.

The question of treatment, of course, seems to be the greatest bugaboo to the general practitioner; that applies especially in the United States and in tropical America. I should have liked to hear Dr. Thomson and Dr. Stephens make some remarks on the treatment of their cases. We all agree here, in this part of the country, that blackwater fever follows malarial attacks — the *Estivo-autumnal*, in the majority of cases at least. According to his remarks, Dr. Thomson's experience with the blood-examination before the blackwater chill, and after, are just exactly what mine has been.

I believe the reason that only a few of the post-mortems show so little evidence of malaria is, that sometimes our patients live for 10 days before death occurs from anaemia or urine suppression. Possibly, if you keep such patients alive 8 or 9 days, they are the very ones that show in post-mortem the least evidence of malarial infection. So we could probably find, in every case that died soon after an attack, the parasites and pigment.

The treatment that I advocated in my paper, in 1909, I have had no reason to change since that time. I advocated the immediate withdrawal of the quinine, as soon as we were convinced the patient had blackwater fever. The reason I did that was, that in my experience I found that for from 24 to 48 hours immediately after the chill it was very difficult to find the malarial parasite in the patient's blood. The malarial parasites always disappear very promptly, though more so in some cases than in others. But we have had one or two cases in which the parasites did not disappear as readily as we thought they should. To those cases we gave quinine hypodermically. There is no use giving quinine by mouth, because vomiting is one of the most pronounced symptoms, and it is difficult for a patient to keep anything on the stomach. Give him plenty of fluids, keeping a blanket over him to prompt perspiration and elimination. We showed 10% death rate with this treatment in a series of 80 cases.

As to the natives' having blackwater fever, I can recall only a few instances; the most frequent cases that we found then, were in imported European laborers, and the shortest period of residence before developing blackwater was 6 months on the Isthmus. The average time of residence on the Isthmus before they had black-

water fever was about 2 years. Within recent years — during the last 8, I may say — we have had very little blackwater fever at Ancon Hospital, probably not over 2 cases a year. I have seen, in recent years, 2 cases in full-blooded negroes and they had blackwater fever as severely as we find it in the white.

What we want is to give the benefit of our experience to the men back in the Bush, who practice medicine. Most parasites will generally disappear within 24 hours; if they do not, I give quinine, but I had experience with 2 cases in which the quinine caused haemoglobinuria. In all cases, with the exception of those two, we began giving quinine by mouth after the urine had been clear of haemoglobin for 6 or 7 days. If you do not do this, many of these cases will relapse, some within 3 weeks, while still in the hospital under treatment for post-haemoglobinuric anaemia.

Dr. José Azurdia. — Dr. Azurdia said that when he left his country there were about 4 or 5 cases of blackwater fever. According to his knowledge, the practitioners there do not believe in using quinine at all in the treatment. Quinine gives most harmful results. They use saline, intravenously and in enemas, with complete success.

He inquired as to the connection between yellow fever and blackwater fever. Dr. Azurdia had had no personal experience with this problem, he stated, and would be very glad to hear the views of the members of the Conference.

Dr. A. A. Facio. — Within the last few years we have had a considerable number of cases of blackwater fever in our hospital in Port Limon, Costa Rica. The treatment we have practiced there, in regard to the administration of quinine, has been that outlined by Dr. Connor — that is, we have administered quinine by intramuscular injection to those cases in which we found the malaria parasites in the blood; and we abstained altogether from administering quinine to those cases in which we could not find the parasites.

Lately Dr. Rojas, one of my associates, and I have been treating all our cases of blackwater fever and paroxysmal cases of haemoglobinuria by administering caffeine sodium-benzoate intravenously, giving two injections daily, one in the morning and one in the afternoon, and the results we have obtained have been remarkably good. Of course, as I said before, we always administer quinine to those cases in whom we find the malaria parasite.

The treatment of blackwater fever is, as we may say, mostly symptomatic, and we always accompany the administration of caffeine sodium-benzoate with the administration of large quantities of saline water, given either by hypodermoclysis or intra-

venously. The purpose is to relieve the most trying symptoms, such as vomiting and excessive thirst, and also to improve the circulation, and thus keep the kidneys flushed. Caffeine sodium-benzoate certainly produces quick and marked effects in improving the condition of all blackwater-fever cases, and it is wonderful to observe how quickly individuals who come to the hospital in an almost moribund state, react to its administration.

This preparation, which is one of the best circulatory stimulants at our command, quickly relieves the hypotension and improves the general circulation and consequently that of the kidneys.

Another report regarding the administration of caffeine sodium-benzoate in cases of blackwater fever, will be published later on when we have studied a greater number of cases.

Dr. H. C. Clark. — I feel highly honored in being called into the discussion of the papers read by Drs. Stephens and Thomson. We have always followed very closely all they have had to say on this subject, and their present work makes me feel all the more keenly how incomplete my observations at autopsy have been.

I am greatly surprised at the small number of "blackwater fever autopsy records" that Dr. Stephens has been able to find recorded in the literature, and I am indeed sorry that the Panama Canal Zone records have not been published. Excluding the cases of haemoglobinuria which occurred during the course of a frank attack of acute malarial fever, we had on record, at Ancon, at the close of the year 1919 just 66 cases of blackwater fever that were examined at autopsy. Circumstances interfered with the publication of these records, but I can give you a few facts concerning 32 of the cases which occurred during the period of time from 1910 to 1913, inclusive. I will tabulate some of the features as follows:

Sex: 28 of them were in males and 4 in females.

Age	*Number of Cases*
9 years and under	2
10 years to 19 years	0
20 years to 29 years	10
30 years to 39 years	14
40 years to 49 years	5
50 years to 59 years	1

Race	*Number of Cases*
Spain	20
Italy	2
Greece	1
Portugal	1
West Indian negroes	7
China	1
Time of Residence on Canal Zone.	
1 year	6
2 years	5
3 years	7
4 years	7
5 years	5
6 years	1
7 years	1

Tissue smears (films) from the spleen pulp and rib marrow revealed malarial parasites in 7 of the cases, and these parasites were aestivo-autumnal (*P. falciparum*) alone or mixed with other types of parasites; 26 of the cases revealed malarial pigment in the marrow, spleen, liver, etc. There were 6 cases in which no parasites or pigment could be found in our routine method of search.

Black-water or "port wine" red-water was found in the bladder at the time of autopsy in 13 cases, while death had occurred in the post-haemoglobinuric stage in 19 cases. There was a very serious degree of anaemia in all of them, and icterus in 24 cases. Inspissation of the bile in the gall-bladder and ducts was noted in 22 cases. Extreme parenchymatous swelling of the organs, especially the liver and kidneys, was always present. The average weight of the organs at time of autopsy was as follows: Brain, 1,360 grams; liver, 1,827 grams; spleen, 555 grams; heart, 311 grams; combined kidneys, 372 grams; right lung, 552 grams; left lung, 493 grams. These are meagre notes, but they are all that I can submit at this time. Perhaps the stimulus given by these papers will continue to exert its influence until I succeed in publishing our entire list of cases in detail.

Dr. Thomson's theory of the cause of the haemoglobinuric paroxysm is a very satisfactory one to keep in mind. I am reasonably sure that blackwater fever, as we see it in our part of the world, is a sequel of aestivo-autumnal malaria (*P. falciparum*). It is more apt to select the foreigner (white race) who comes to the Tropics, than the negro or Central American native, but the latter races are not entirely immune, as experience in Honduras has already shown me.

For those who still hold to the belief that blackwater fever is a disease *per se* and is only found accidentally associated with malarial fever because of the high rate of the latter disease in the Tropics, there are a few cases which might seem to substantiate their claims. I might mention a dual infection that occurs in cattle. Acute bovine piroplasmosis is quite like malaria, and is frequently associated with haemoglobinuria that is certainly the direct result of the disease. Yet in about 10% of the acute cases of piroplasmosis in imported non-immune cattle, I have been able to demonstrate an acute spirochaetosis proceeding at the same time. The latter is not a serious condition.

It was this fact, together with a theory expressed some years ago by Dr. Sambon, regarding the cause of haemoglobinuric fever, that led me to investigate at autopsy all cases of blackwater fever. The chief method used was silver-staining of the tissues, but many were also subjected to dark-field examinations of the blood and urine. I never found a spirochaete in the human cases of haemoglobinuric fever.

I do not believe there is a dual infection in these cases or that blackwater fever is a disease apart from aestivo-autumnal malaria. The fact that a patient *suddenly drops* to a haemoglobin index of 10 to 20% and loses enormous numbers of red cells is sufficient reason, in my opinion, for the failure in many cases at autopsy to find parasites. The red cell is the home of the parasite, and the parasites must to a very large extent disappear when the onset of severe haemoglobinuria occurs. The pigment remains.

Dr. J. W. W. Stephens (*Closing the Discussion of his own and Dr. Thomson's papers*). — Dr. Stephens said that this had been a most disappointing discussion, for, instead of developing a raging diversity of opinion, it had revealed an almost complete unanimity! He discussed the question of urobilinuria, and whether susceptibility to attack could be estimated from this condition. The malaria factor, said Dr. Stephens, could be computed by collecting, say, 1,000 cases of people who had certainly not had malaria for one or two years, and by observing whether blackwater occurred among them. From the laboratory standpoint, he emphasized, it was not possible at present to advise as to whether or not quinine should be given. This is for the clinician to decide, and the clinician could still with advantage describe his findings, as there are still many lacunae in our knowledge.

Dr. J. G. Thomson, (*Closing the discussion of his own and Dr. Stephens' papers*). — In regard to Professor Stephens' remarks, I need only say that when we read his paper we shall have one of

the most complete criticisms of the whole literature on the subject, and naturally it will be an extremely valuable contribution. Professor Fülleborn made an interesting observation: namely, that blackwater fever was extremely rare among the German troops in Macedonia, whereas in the British Army this disease was common.

Dr. Castellani's attempt to class blackwater fever in three different types seems to me, from all the available facts, to be unnecessary. In my opinion, there is no difference between the clinical conditions of quinine haemoglobinuria and those of blackwater fever. The symptoms are the same. I do not believe we should classify these conditions as separate entities. As regards blackwater fever's being a specific disease, I might speak in regard to some remarks Dr. Clark made. If Dr. Clark will publish some of these post-mortem findings, he will give us a valuable contribution to the literature. Like Dr. Clark, I was quite unable to demonstrate the spirochaetes, either in the tissue or in the blood. The fact, however, that we do not find the spirochaetes in all cases, does not mean they are not there. There is no doubt that pernicious malaria is the primary causal factor of this disease. The fact we cannot demonstrate the parasites in all cases *does not mean they are not there.* In regard to treatment, Dr. Connor and others know more than I do. Dr. Daniels, many years ago, said there was no known specific treatment, and this statement holds good today.

AMERICAN ANOPHELINE MOSQUITOES, THEIR CLASSIFICATION AND THEIR RELATION TO THE TRANSMISSION OF MALARIA

FRANCIS M. ROOT, PH.D.

Since, for several years past, I have been engaged, mainly from the taxonomic viewpoint, in the study of the American Anopheline mosquitoes, it occurred to me that it might interest the delegates to this Conference to hear a brief résumé of the present classification of these mosquitoes, together with a summary of what is at present known regarding the relation of the different species to the transmission of malaria.

With a single exception, the Anopheline mosquitoes of North, Central, and South America may all be included in the genus *Anopheles*. This genus is now usually considered as containing three subgenera, of which one (*Myzomyia*) is confined to the tropics and the sub-tropics of the Old World.

Of the two subgenera represented in the Americas, the more primitive (subgenus *Anopheles*) includes practically all the North American species, as well as a group of large and profusely ornamented species characteristic of the American tropics, and a few other aberrant (and usually rare) tropical forms. This subgenus is well represented in both the temperate and the tropical portions of the Old World. The third subgenus (*Nyssorhynchus*) is confined to the American tropics, and includes the most common and dangerous Anophelines of this region.

Although the American Anophelines are ordinarily classed in these two different subgenera, characterized particularly by the structure of the male genital apparatus, they can all be arranged in a single series, which probably represents, as well as can be represented by living species, the course of the evolution of the group. In other words, I think there is little doubt that the species of the subgenus *Nyssorhynchus*, of which *A. albimanus* is a good example, have evolved from species which would be classed in the subgenus *Anopheles;* and I believe that traces of a connection between the two groups can be seen today in some of the species of that pro-

fusely ornamented group of Anopheline mosquitoes which Theobald divided between his so-called genera, "Arribalzagia" and "Cycloleppteron."

If we arrange the American Anophelines in such a series (Table I), we can recognize among them not only the two subgenera already referred to, but six fairly well-defined groups of species, corresponding roughly to the "genera" of Theobald. Beside these definite groups, there are also a few aberrant species, which seem to be, in a sense, connecting links between some of the groups.

The first two of these groups, which we may call the Anopheles group and the Patagiamyia group, include all the characteristic North American Anophelines, together with a few, mostly rare and unimportant, tropical species. The Anopheles group includes only species with dark wings, like *A. quadrimaculatus*, while the species of the Patagiamyia group have wings with comparatively few, but very distinct, light areas, as in *A. crucians* and *A. punctipennis*.

The third, or Arribalzagia, group is the largest of all, in number of species. It, together with two related species, is distinguished from all other groups of American Anophelines, because of a peculiar fragmentation of the wing pattern, resulting in the occurrence of numerous small, alternating, dark and light spots. This marking is particularly pronounced on the sixth vein, where we find from four to eight discrete dark spots, whereas in species of other groups the maximum number is three. This Arribalzagia group occurs all over the American tropics, although the South American species are different from those of Central America.

The other three groups, composing together the subgenus *Nyssorhynchus*, may be dismissed rather briefly. The type group of the subgenus, the Nyssorhynchus group, which includes such familiar species as *albimanus*, *argyritarsis*, and *tarsimaculata*, is found throughout the American tropics. In Brazil there are three other species which may tentatively be separated as the Myzorhynchella group, although they have not been sufficiently studied to enable me to make any dogmatic assertion as to the distinctness of this group. And finally, the peculiar and variable Anophelines that breed in the leaf-bases of epiphytic bromeliads, or "wild pines," undoubtedly constitute a group by themselves, which may be called the Dendropaedium group.

Now, as to the relations of the various species to the transmission of malaria. If we search through the published literature, for detailed studies on the susceptibility of American Anophelines to experimental infection by the malaria parasites, or for careful records of the percentages of "wild-caught" females that are infected, we find such data rather scanty (Table II).

In North America there are fairly satisfactory data on the three common eastern species. Summarizing together the results of Mitzmain, King, Woldert, Hirshberg, and Beyer and his associates, we find that, experimentally, *A. quadrimaculatus* can be infected with all three species of malaria parasites, in percentages large enough to indicate it as an important carrier; while, taking the published data at their face value, *A. punctipennis* should be a good carrier of tertian malaria, but not of estivo-autumnal; and regarding *A. crucians*, just the reverse should be true. When we turn to records of natural infection, which, after all, are the most trustworthy, we can find records of the examination of nearly 9,000 wild-caught females of *quadrimaculatus*, with an average natural infection of almost 1½%. Of *punctipennis*, only one infected specimen has been recorded out of about 543 examined, while *crucians* can boast three infected specimens out of 1,203. The percentage infected, in both of these species, is very markedly lower than in the case of *quadrimaculatus*. This may possibly be explained by the food habits of these two species. Preliminary reports by Bull — in coöperation with King and with Darling — on the identification of the blood meals of Anophelines by the precipitin test, indicate that *punctipennis* and *crucians* feed on horses, cattle, and other domestic animals to a much greater extent than does *quadrimaculatus*.

Turning to Central America, we have the extensive experimental infections of Darling, at Panama, indicating that *albimanus* and *tarsimaculata* are dangerous carriers, while *pseudopunctipennis* is of much less importance, and *punctimacula* (*malefactor*) could not be infected at all. Darling also records finding a natural infection in *argyritarsis*, and I am informed that natural infections have been found also in both *albimanus* and *grabhamii* in Porto Rico.

In South America very few exact data are available. Galli-Valerio found oöcysts in one out of twenty alcoholic

specimens of *A. bellator* from the state of Paraná, Brazil. Considerable work on experimental infections has evidently been done by Neiva, Gomes de Faria, Ruy Ladislao, and others, but the full data are not accessible. According to Neiva's brief summary, experimental infections have been produced in *argyritarsis*, *tarsimaculata*, *pseudomaculipes*, *intermedium*, and *mediopunctatum*. I understand that recently natural infections have been found, too, in *argyritarsis* and *tarsimaculata*.

To sum up, the evidence at hand indicates that in North America two species of the Anopheles group (*quadrimaculatus* and *maculipennis*) are the principal malaria-carriers, with species of the Patagiamyia group (*punctipennis*, *pseudopunctipennis*, *crucians*) playing a very subordinate part. In Central and South America, the principal carriers belong to the Nyssorhynchus group (*albimanus*, *argyritarsis*, *tarsimaculata*) while species belonging to the Patagiamyia, Arribalzagia and Dendropaedium groups have been less definitely incriminated (Table III).

In conclusion, I would like to make a plea for more dissections of wild-caught Anophelines, in search of the malaria parasites; more publication of such results, even though they be negative; and especially, for more practical experiments to determine whether it may not be possible to control malaria by applying control measures only to those two or three species of *Anopheles* in any locality, which are already known to be dangerous carriers of this disease.

TABLE I

CLASSIFICATION OF AMERICAN ANOPHELINE MOSQUITOES

Genus Chagasia ..... C. fajardoi

Genus Anopheles:

Subgenus Anopheles.....	*A. nimbus*	Anopheles group
	A. barberi	
	A. atropos	
	A. walkeri	
	A. quadrimaculatus	
	A. maculipennis	
	A. eiseni	Patagiamyia group
	A. crucians	
	A. punctipennis	
	A. pseudopunctipennis	
	A. mattogrossensis ?	
	A. gilesi ?	
	A. grabhamii	
	A. annulipalpis	
	A. amazonicus	Arribalzagia group
	A. vestitipennis	
	A. apicimacula	
	A. punctimacula	
	A. strigimacula	
	A. maculipes	
	A. pseudomaculipes	
	A. intermedium	
	A. mediopunctatum	
	A. peryassui	
Subgenus Nyssorhynchus	*A. lutzi*	Myzorhynchella group
	A. parva	
	A. nigritarsis	
	A. albimanus	Nyssorhynchus group
	A. tarsimaculata	
	A. argyritarsis	
	A. braziliensis	
	A. pictipennis	
	A. bellator	Dendropaedium group
	A. boliviensis	

TABLE II

INFECTION INDICES OF AMERICAN ANOPHELINE MOSQUITOES

		Number dissected	Number infected	Percent infected
North America				
Experimental infections:				
A. quadrimaculatus	tertian	43	14	32
	estivo-autumnal	161	37	23
	quartan	5	2	40
A. punctipennis	tertian	47	19	40
	estivo-autumnal	351	19	5
A. crucians	tertian	21	2	9
	estivo-autumnal	15	10	67
	quartan	3	0	..
Natural infections:				
A. quadrimaculatus		8,864	130	1.47
A. punctipennis		543	1	0.18
A. crucians		1,203	3	0.25
Central America.				
Experimental infections:				
A. albimanus	tertian	7	6	85
	estivo-autumnal	43	30	70
A. tarsimaculata	estivo-autumnal	5	3	60
A. pseudopunctipennis				
	tertian	4	0	..
	estivo-autumnal	27	4	15
A. argyritarsis	tertian	1	0	..
	estivo-autumnal	3	0	..
A. punctimacula	estivo-autumnal	17	0	..
Natural infections recorded, without exact data, for:				
A. grabhamii				
A. albimanus				
A. argyritarsis				
South America				
Experimental infections recorded, without exact data, for:				
A. argyritarsis (tertian and estivo-autumnal)				
A. tarsimaculata (tertian and estivo-autumnal)				
A. pseudomaculipes (estivo-autumnal)				
A. intermedium (estivo-autumnal)				
A. mediopunctatum				
Natural infections:				
A. bellator		20	1	5
Natural infections also recorded, without exact data, for:				
A. argyritarsis				
A. tarsimaculata				

TABLE III

AMERICAN MALARIA-CARRYING ANOPHELINES

I. Species proved to be susceptible to infection with the malaria parasites.

1. Species known to be important carriers of malaria:
   - *A. quadrimaculatus*
   - *A. maculipennis*
   - *A. albimanus*
   - *A. tarsimaculata*
   - *A. argyritarsis*

2. Species proved to be susceptible to infection, but believed to be less important than the above species:
   - *A. crucians*
   - *A. punctipennis*
   - *A. pseudopunctipennis*
   - *A. grabhamii*
   - *A. pseudomaculipes*
   - *A. intermedium*
   - *A. mediopunctatum*
   - *A. bellator*

II. Species suspected of transmitting malaria on epidemiological grounds.
   - *A. nimbus*
   - *A. lutzi*
   - *A. parva*
   - *A. braziliensis*

DISCUSSION

Dr. Henry Rose Carter (*Opening the Discussion*). — He said he could present some data on the effect of controlling one species of Anopheles only: —

In Chester, South Carolina, a history index of malaria was taken and 7% of the population were found to have had malaria. A careful survey was made and Fisher, a careful man, found nothing but *punctipennis* around Chester. Boldridge and Fisher "trained" the streams about Chester so as practically to eliminate breeding. The next year no malaria showed, except cases that had had it the preceding year. *Punctipennis* had then been an efficient vector of malaria.

About Bridgewater, N. C., there was an outbreak of malaria, around a large pond. After making an examination of the pond and in the vicinity of the houses — about 20 days in all — I found nothing but *punctipennis*. Nor did Fisher find any thing but

punctipennis. Le Prince was there for about a week, and he could not find a single *quadrimaculatus.*

In Greenville, S. C., in 1912, there was a considerable epidemic of malaria, — about 1,400 cases. The following year it was reported that of about 1,100 imagos captured, and developed out from larvae, all except one were *punctipennis.* This epidemic must have been caused by *punctipennis.* Some years ago I attempted to investigate the proportional role of the different species of Anopheles we have in my part of the United States: — *quadrimaculatus, punctipennis,* and *crucians.* I am inclined to modify my opinion that *punctipennis* is not an efficient vector in nature, although I think it is less efficient than *quadrimaculatus.* As to *crucians:* A considerable part of the rural, tide-water section of Virginia is decidedly malarious, and is for the most part uninhabited by white people. Practically the only anopheles breeding in this country is *crucians,* although both of the other species occur to some extent. But I am sure that Anopheles *Crucians* conveys malaria, and conveys it efficiently, in this section.

Dr. F. M. Root (Closing the Discussion.) — He said he would like to make one point in regard to Anopheles *crucians,* or rather to suggest a theory of his own. "I believe," he said, "that Anopheles *crucians* occurs in two races or strains, one breeding in brackish water and one in fresh water. Morphological differences between the larvae of the two races have been found. Larvae collected far inland in Lee County, Ga., and in the marshes of the Chesapeake Bay show this difference. In our work in Leesburg, Ga., we found no infected specimens of *crucians.* I think it is certainly worth investigating to see whether it is not possible that the brackish water variety of *crucians* may be an efficient carrier of malaria while the fresh water variety is not."

CAN WE GET BETTER ANOPHELES-CONTROL AND MORE MALARIA-CONTROL AT LESS COST?

J. A. LePrince, C.E.

The writer was recently occupied with yellow-fever-control measures on the coastal plain of Mexico, and noticed that many of our petroleum corporations are so busy obtaining oil that they take practically no precautions to control malaria, even where half their labor force or more are affected by malaria. Their financial losses from this cause are probably ten times the cost of what the preventive measures would be. Up until a few years ago, there was a similar condition in some of our southern states.

One of our problems, therefore, is to learn how to prevent business corporations from wasting their own funds. In solving this problem, it may be necessary to determine a means of measuring the labor turnover and its cost, and the number and percentage of "man days" lost as a result of malaria fevers; and also to obtain a comparison of output between similar-sized forces of labor, where one is affected by malaria, and the other relatively free from this disease.

We have considerably increased the output of some industries in our southern states, through malaria elimination, but we have not yet taught most of our business men with financial interests that it is folly to attempt development of natural resources in malaria countries, without taking proper precautions.

It is not unusual for men of good executive ability to consider applied sanitation a non-essential. Possibly it is true that sanitarians are often poor salesmen; and there is no doubt that, with a few brilliant exceptions, we have failed to impress on the minds of our public, and upon those who develop natural resources, that malaria uncontrolled means financial loss.

We do not achieve that state of malaria-control which we should obtain, because we fail to make the public want it and work for it. The desire for freedom from malaria *can* be created, and it is well worth while to work toward that end.

It takes time, hard work, and enthusiasm to bring it about, but it *can* be done. Our people have not yet caught the idea that they are paying the bill, directly or indirectly, and getting nothing in return. They will never want what they don't understand, nor will they be ready to pay for it, so the sanitarian sooner or later must learn how to teach and how to convince.

In the United States, we find that the public pays the screen manufacturers about $25,000,000 a year for mosquito screen-wire to protect their homes. But this protection is only partial. Too many buildings that are screened are either not effectively screened, or else the screening is not effectively maintained. The financial investment is made, but owing to neglect or lack of interest, the screening is too often ineffective. After a building is screened, it should be inspected for places through which Anopheles can enter, and any necessary alterations should be made. All screened buildings should be inspected at definite, short intervals, and defects should be remedied promptly when noted.

In areas where malaria prevails, Anopheles that gain access to screened buildings can be found on the screen in the early morning, and again at dusk, at which times it is easy to destroy them.

Even in buildings that are not screened the gorged Anopheles resting on the walls are easy to kill during the daytime with a fly swatter; and when the family is interested, they destroy nearly all these potentially-infected Anopheles. This systematic destruction can be achieved even in the homes of the poorer classes; the children like to help. And where the procedure is systematically carried out, it has a tremendous influence on preventing malaria transmission. It has been tried and proved very successful.

The mosquito traps used on the Isthmus of Panama proved to be effective in Anopheles-elimination. Anopheles select daytime resting places that are protected from bright light and from air currents; and there is no reason why such places should not be created and treated with cheap tangle foot "compounds," so that the potentially-infected and other Anopheles will destroy themselves by dozens. This plan, too, has been tried, and it works.

Boxes placed bottom upward, and with one side removed are desirable collecting places for Anopheles *quadrimaculatus*,

and possibly also for other species. Place them in the shade near potential breeding places and near wet areas under control, to measure Anopheles-production and control-efficiency, respectively. Such boxes, if treated, will prove to be final resting places.

Where Anopheles rest under houses, similar modified treatment can be used. It certainly will be worth while to make them destroy themselves at both terminals of their flight range. It appears essential for us to study their habits, likes, and dislikes more closely, and then determine in what way we can make practical use of the information thus gained. There is also no reason why some artificial breeding places (such as bodies of water) that are attractive to them, can not be created, and used as egg-collectors. The water in such places can be treated so that the eggs will not hatch; or we could use suitable confined floatage, depress it at short, definite periods, and permit small fish to destroy the larvae.

Top minnows and other suitable fish have not been used as much as they should be. Hildebrand determined that, under natural conditions, and with considerable aquatic vegetation present, Anopheles larvae are reduced 80%, where there are large numbers of Gambusia *afinis*. These fish breed very rapidly, and often can be utilized in the place of larvicides or oil. Frequently, it is not so costly to remove enough of the aquatic vegetation from time to time, to make the fish control satisfactory, as it is to apply larvicides. In relatively large bodies of water of intermittent character pits can be dug at low spots to collect these fish, so that they will survive the dry period. When our work is far from our base of supplies, it is convenient to have something to substitute for the larvicide when the supply runs short.

The food of Anopheles is an item in which we should be more interested, since, by its control we can create a more economical procedure.

We now know that Anopheles readily devour small floating particles of Paris green, and that a dust cloud containing 1% of Paris green effectively controls Anopheles-production in bodies of water with much aquatic vegetation.

Paris green treatment is effective for destroying Anopheles larvae, and at the same time it does not harm fish or other forms of aquatic life. A combination of fish-control supple-

mented with the Paris-green dust-cloud treatment, in some instances is much more economical than any other known control measures. Floatage and algae are the main factors that interfere with effective fish-control. Instances have occurred in which a reduction of 60% in control costs have been accomplished by using top minnows, as compared to 80% by using Paris green as a control agent.

There are many places which appear to be favorable to Anopheles production, but which in reality are of little sanitary importance. Also we find bodies of water only a small portion of which do actually produce malaria mosquitoes. In such cases, where drainage is expensive, the need of a detailed survey by a person well qualified to judge what should be done, and how it can be done most economically, is self-evident. In one instance, in my personal experience, the engineering corps of a certain railroad made an estimate of $4,000 for draining a swamp, but could not state how soon the work could be completed. We blew out a ditch of the proposed size, by dynamite, in a period of six days, at a cost of $900. This cost, by the way, included the traveling expenses of two engineers, and the expense of making a moving picture film. After we had made the first test "shot" of 900 feet, nothing would satisfy the railroad but to send for the higher officials to witness the work under way, and thus break down our efforts to reduce costs.

In another instance an engineer gave an estimate of $11,000 for drainage work that subsequently was completed at an actual cost of only $1,200. In this case, the question of size of ditch was involved. It is to be noted that in drainage for malaria work, it is not essential that areas be "dewatered" rapidly. Often water may be allowed to stand for one day (or more) if necessary, so far as Anopheles drainage is concerned; for agricultural or other purposes it may be desirable to remove it in the same number of hours. In carrying out our Anopheles drainage and anti-malaria work, we should *not* do anything that is unessential. For example, we should not use three big ditches, when two smaller ones will serve the same purpose. On the other hand, we *should* do everything that will rid us of Anopheles. In some cases it is best to treat breeding places at definite intervals; in other instances it is more economical to make frequent

inspections of the areas involved, and treat only as the findings indicate treatment is necessary. A very large part of the success of the work depends on the personal interest, experience, and activity of the person directing field operations.

Improvements in procedure, resulting in reduced costs, are being devised. Some of them have been referred to. But we appear to lack force and initiative in selling to the public involved the idea of saving expenditures, by spending the equivalent of a fraction of their losses due to malaria, in order to eliminate it and change those losses into profits.

DISCUSSION

Dr. Henry R. Carter (Opening the Discussion). — I scarcely know what to discuss in Mr. LePrince's paper. He has asked the question, "Can we get better Anopheles control and more malaria control at lower cost?"

In the United States we place great stress on the economic value of malaria control, perhaps more than on its sanitary value. The first place where we attempted to do malaria-control work was Roanoke Rapids, North Carolina, in the fall of 1913. That territory was scourged by malaria. I think it is safe to say that once a year every person in the locality was afflicted with malaria — the simple tertian type mainly. When the blood was examined 32% of the population were found to be positive. We did the work at about $1.05 a head, and saved about 10 times that amount. It was not paid for by the people; it was paid for by the business men who had cotton mills, paper mills, etc., in the territory.

The Mayor told me that, although they had good electric power, very cheap, and although several companies had taken out options on land before our control work was undertaken, they had forfeited these options when they saw how the laborers were affected by malaria. One year afterward, the index was reduced from 32% to 2%. The owners of the two largest cotton mills said, "We are business men, and have been in the habit of putting out our money only when we can get a good return, but never before have we received so good a return as we have from this malarial-control work."

A considerable amount of similar work has been done in other places. We have attained very much better success by going to small towns where there are large factories — as at Crystal City, Missouri, and Electric Mills, Mississippi — and getting the business men to understand that it will pay them to do anti-malaria work in the community. We don't speak of the elimination of

malaria, but if you can reduce its prevalence from 50% down to 5% in a year, or even to 2% or 0.5% — and that can be done — you control the disease. If we can get a place in which the business men are interested in having work done, and if the men we send there know the facts about malaria, we can nearly always raise sufficient funds for malaria control; and the work has always been successful from a financial point of view. In the south of the United States, many business men are in the habit of spending $100,000 to get $150,000, but the municipality does not like to spend $100,000 no matter what are the returns. Go to that business man himself, and in 99 cases out of 100 you will be able to secure funds for malaria work.

At the last meeting I attended of the National Malaria Committee, for the existence of which Mr. Frederick L. Hoffman is responsible, and which is a kind of clearing house for reporting control of malaria in the United States, it was reported that the number of square miles that were under control was large — I forget the figures — and that the number of persons protected in this area was also large. The work has been going on, now, for some years, and I think that no community that has tried to secure elimination of malaria by means of mosquito control, has ever discontinued the effort.

In addition, many side lines have been followed. We started with one railroad in 1917, showing them that it was to their advantage to do malaria work along the right of way and in their shops. There now are four railroads that are employing sanitarians. For some years we worked upon malaria at the ponds of hydroelectric plants. Within the last year, three of these companies have employed men regularly as sanitary officers, but really all these officers do is to attempt to control malaria. If such efforts should become general — and they would really mean an economy — a great deal of malaria would be prevented.

There is much "man-made" malaria with us, and many communities are fighting it. This fight is not carried on in a spirit of altruism, although I hope that that plays a part, too. We still have a great deal more, however, to do in the United States. What we have done is considerable, but it is small in proportion to the amount yet to be done. Naturally there is an increase in malaria work each year. The present generation will see malaria pretty fairly under control, but I think never *eliminated* in the United States. We try to *eliminate* yellow fever. We are satisfied with the *control*, *i.e.*, a sufficient reduction, of malaria.

Dr. Seale Harris. — Mr. LePrince spoke of a method of trying to prevent corporations from wasting their money, in failing to provide sanitary environment for their employes. I should like

to mention one corporation in Alabama and the results they have obtained not only in malaria control, but in the care of their employes and in the prevention of disease among them. That organization is the Tennessee Coal and Iron Company of Birmingham, a subsidiary of the United States Steel Corporation.

The firm employs 35,000 people, and provides for the medical care of 100,000 people — that is, employes and their families — in the district. Some twelve years ago, Mr. George Gordon Crawford, the president of this company, made a trip to Panama and the Canal Zone. While there he was impressed, he told me, by the fact that the laborers of the Canal Zone appeared to be in better physical condition than those he had known in Bethlehem and in Alabama. He therefore decided it would be good business for the Tennessee Coal and Iron Company to spend some money to prevent disease among their employes.

His first step was to secure the services of Dr. Lloyd Noland whom many of you knew in the Canal Zone. Dr. Noland came to Alabama ten or twelve years ago, and began organizing the work of the Medical Department of the Tennessee Coal and Iron Company. During the first year of this work, there were more than 2,000 cases of malaria. In less than five years, immediately afterward, among 90,000 to 100,000 persons — employes and their families — there were less than 150 cases. (And by the way, the Company provides for the physical examination of every one of their employes before they enter the service, and annually during employment. They also look after the nutritional problem, provide dental clinics, and in other ways cure and prevent disease.) Mr. Crawford states his belief that it is good business to spend money to prevent disease.

I spoke this morning about the great reduction of malaria in Alabama, and I am afraid I may have been misunderstood as saying that the use of quinine was entirely responsible for it. It is responsible for it partly, perhaps more than any other one measure. But during the last 25 years there has been a great increase in the interest taken in public health, in Alabama, and much work has been done on mosquito control. The Rockefeller Foundation, 20 years ago, gave $5,000,000 toward the eradication of hookworm in the South. In my judgment that was the most important thing that has been done for the South in this generation. It opened the eyes of the people regarding conditions. The campaign involved not only concerted efforts against hookworm, but also malaria control, as well as a campaign against typhoid fever, which has been reduced enormously. When the Rockefeller Commission work began, $25,000 was spent in behalf of 2,000,000 people throughout the State of Alabama, an area of 50,000 square

miles. Today the State appropriates in the neighborhood of $200,000 annually, for public-health work. There are 16 counties in which there are full-time health officers and complete health units. Birmingham now contributes $75,000 a year, and Jefferson county $75,000. I may say, also, that we shall never forget what the United States Public Health Service has done in Alabama. Dr. Carter, dean of tropical medicine in the United States, advised us regarding malaria control; Dr. von Ezdorf also did an enormous amount of work relative to malaria; Mr. LePrince has come to us often; and we are trying to profit by their advice.

Mr. J. A. LePrince (*Closing the Discussion of His Paper*). — I think the most encouraging feature of the work that has taken place, is the coöperation of our general rural population and of the farmers, in improving the screening of their houses, and ditching their own lands. They are doing their own malarial drainage, and as soon as our farming populations succeed at this task, malaria is going to be rather scarce.

SUGGESTIONS FOR THE CONTROL OF MALARIA ON THE PLANTATIONS OF THE UNITED FRUIT COMPANY

H. R. Carter, M.D. and J. A. LePrince, C.E.,

These suggestions refer particularly to the control of malaria among the colored and native laborers employed by the United Fruit Company and living in quarters under its control. They may be discussed under the following headings:

1. Prevention of Anopheles-production insofar as this is economically practicable.
2. The use of repellents around the quarters of employes.
3. Daily hand-killing of Anopheles in quarters.
4. Freeing from infection those employes treated for malarial fever.

1. Prevention of Anopheles-production

Since cost has to be considered, it is impracticable to carry this method out fully. We must therefore select those breeding places where the results of control justify the cost.

The *advisability* of the control of any particular breeding place, then, should depend on (1) the cost of its control, and (2) the amount of malaria it will produce if not controlled.

The Cost of Control depends on the nature of the breeding place, the surrounding topography, prevailing wages, and other factors determinable only by the man on the grounds. The item of up-keep must be considered in estimating the cost of control.

The Amount of Malaria caused by a breeding place depends mainly on the following factors:

(*a*) Species of Anopheles produced.
(*b*) Number of Anopheles produced.
(*c*) Proximity of breeding place to quarters.

(*a*) *Species of Anopheles.* — Naturally a place producing a species that is an efficient vector of malaria, causes more malaria than one producing an equal number of a less efficient vector.

On the Canal Zone, *A. albimanus* and *A. tarsimaculata* (both are *Cellia* in Theobald's classification) were certainly our principal, possibly our only serious, vectors of malaria. They were very abundant, easier to infect than the other species, much more generally found in houses, and capable of long flights.

If the species of Anopheles on the plantations are the same, and present the same biology, as on the Canal Zone, and if we have to differentiate between the control of the production of the different species, it would be advisable to give precedence to control of places producing these two species — *i.e.* to concentrate on them. It would seem advisable to determine the species most prevalent on the different plantations, as not all of them may show the same species of Anopheles, — or the identical species of Anopheles may not show the same characteristics as those on the Canal Zone; a regional variation in the biology occasionally occurs.

Places close to the quarters producing in large numbers Anopheles known to be efficient vectors of malaria, should have precedence of control, and especially if this control is not costly. In the season of maximum Anopheles-production (or of maximum infected-Anopheles prevalence) we should know whether the species involved has any tendency to collect in any preferential place. At Gatun, Anopheles was often found in ground cracks under houses. We should determine the preferential collecting and resting place of the Anopheles involved.

(*b*) *The number of Anopheles produced.*—This needs no discussion.

(*c*) *Proximity of breeding places to quarters.* — Although we cannot assert that the amount of malaria produced at any one place is always proportional (inversely) to its distance from the breeding place of the vectors causing it, the proximity of the breeding place to quarters is, of course, one factor in the accessibility of the Anopheles produced from this breeding place to the men we wish to protect. Hence, it is a direct factor in malaria-production, with which might be included a number of others, such as intervening woods, hills, and groups of residences, the direction, time of day, and strength of winds, screening of quarters, etc. All of these things must be considered by the man on the grounds,

but the data concerning most of them are decidedly unsatisfactory; and certainly, to discuss them would make this memorandum, intended to be simple, unduly complicated.

2. The Use of Repellents About the Quarters

This method is suggested tentatively only. It is cheap, and the results reported by Coogle, in the Mississippi Delta, were good. It is suggested that information concerning this can be obtained from the Bureau of the United States Public Health Service, Washington, D. C.

3. The Daily Hand-Killing of Anopheles in Quarters

This gave good results in the Canal Zone and at the Reservoir at Camp Eustis, Va. Men skilled in finding the Anopheles would be necessary, in the beginning. Whether the people living in the house, after being taught to find the insects, could be trusted to keep the house free of them, is a question. It would be a great advantage if they could, but even if this searching has to be done in perpetuity by men paid by the Company, it still ranks as a method cheap in proportion to its efficacy.

Boys of 13 to 16 years or less make generally better mosquito catchers than grown men of the laborer class. If the wage is so arranged that there is slight addition (say 20% increase in pay) where 100% control is effected, we are much more apt to get 100% results. The cost, even then, is less than the cost of employing mature laborers and the results are better.

The cost depends on the amount of work to be done. To reduce the cost of the drainage or larvicidal treatment, we can try by staining and glass plates ("stickum") to see which areas producing Anopheles are actually involved. By "stickum plates" are meant plates of glass covered with a mixture of resin and castor oil, to which any insect, coming in contact, will adhere. If these are set at different angles we can determine the *direction* of *flight* of mosquitoes, and hence usually locate their place of origin. Thus, if two plates with sticky surface on both sides were set up, one facing North and South (the plate ranging East and West) and the other a few feet off, at right angles to the first, *i.e.* its sticky surface facing East and West) — if we found many Anopheles caught on the North side of the first plate, with a

practical absence of them on the South side of the plate, and no mosquitoes adhering to Plate No. 2, we should know that the flight of the mosquitoes was from the North only. If we found approximately the same number of mosquitoes on the North face of Plate No. 1 and on the East face of Plate No. 2, the flight would be indicated as about Northeast.

By this means we can tell quite definitely (not absolutely, it may be) the source of the Anopheles mosquitoes coming into camp. Griffith adopted for this purpose sheets of celluloid about 3 x 3 feet, used in the manufacture of automobiles.

4. Freeing from Infection Employes Treated for Malarial Fever

This will quite frequently be impossible, — the patient refusing or failing to continue proper treatment long enough. Yet with the greater resistance of negroes to malaria, cure possibly would be less infrequent than our observations on white men have led us to expect. Here, too, there is need for research, and in a virgin field.

The regular administration of quinine to healthy people to immunize them against the bites of infective Anopheles, is not recommended except in a temporary emergency when the exposure to a malignant malaria is very great, — as in the case of gangs opening up new lands, the occurrence of an unusually severe and general epidemic of malaria, etc.

EXPERIMENTAL STUDIES OF YELLOW FEVER IN NORTHERN BRAZIL

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Yellow fever is known to have existed in Brazil[1] from the beginning of commercial development of the country until it was practically eradicated by the vigorous anti-mosquito campaigns of Oswaldo Cruz, Ribas, and Lacerda. In certain limited areas, in the states of Ceará, Bahia, and Pernambuco, the disease was still present during 1922 and 1923.

While there was no reason to regard the yellow fever of Brazil as different from that occurring elsewhere, the microorganism isolated from cases of yellow fever in Ecuador[2], Peru[3], and Mexico[4] had not been experimentally demonstrated as the cause of Brazilian yellow fever. Hence an investigation into the etiological relation of *Leptospira icteroides* to cases occurring in Brazil was undertaken by a joint commission of Brazilian and American workers, the latter having received an invitation from Dr. Carlos Chagas, Director of the Departamento Nacional de Saúde Publica, to make an expedition to Brazil under the auspices of the International Health Board of the Rockefeller Foundation. The experiments covered the period from November 29, 1923, to February 24, 1924, and were carried out at the Oswaldo Cruz Institute, of Bahia, — the staff of the In-

[1] BOYCE, R.; "Yellow Fever and Its Prevention," New York, 1911, p. 11.

[2] NOGUCHI, H.; *Journ. Exper. Med., 29:* 547, 565, 585 (June), 1919; *30:* 1, 9, 13, 87, 95 (Aug.), 1919; *30:* 401 (Oct.), 1919; *31:* 135, 159 (Feb.), 1920; *32:* 381 (Oct.), 1920; *36:* 357 (Sept.), 1922. COHN, A. E., and NOGUCHI, H., *Ibid., 33:* 683 (June), 1921. NOGUCHI, H., and PAREJA, W., *Journ. Am. Med. Assn.. 76:* 96 (Jan.), 1921.

[3] NOGUCHI, H., and KLIGLER, I. J.; *Journ. Exper. Med., 33:* 239, 253 (Feb.), 1921.

[4] NOGUCHI, H., and KLIGLER, I. J.; *Journ. Exper. Med., 32:* 601, 627 (Nov.) 1920. PEREZ GROVAS, P., *Journ. Am. Med. Assn., 76:* 362 (Feb.), 1921. A strain of *Leptospira icteroides* was also isolated by Dr. Thomas J. Le Blanc, in Vera Cruz, in 1920.

stitute, the Faculty of Medicine, and the State and Federal Departments of Health being represented on the commission.

The special equipment for the work was taken from the Rockefeller Institute, including microscopes, sterile glassware of all kinds, filters, sterilizers, incubators, and iceboxes. Four hundred guinea pigs were also taken from New York as well as 50 rabbits to furnish serum for culture medium, 4 *Macacus rhesus* monkeys, and 3 baboons. About 100 marmosets, 3 "prego" monkeys (*Cebus macrocephalus*) and a black spider monkey (*Ateleus ater*) were purchased in Bahia.

The plan of the work involved (1) the isolation of *Leptospira icteroides*, (2) the reproduction of yellow fever in lower animals, (3) the demonstration of the Pfeiffer reaction for *Leptospira icteroides* in the serum of persons recovered from yellow fever, and the absence of such a reaction in the case of *Leptospira icterohaemorrhagiae*, (4) the proof of the filterability of the Brazilian strains of *Leptospira icteroides*, and (5) the determination of the protective property of the anti-icteroides immune serum (horse) prepared by means of other strains of *Leptospira icteroides* against infection with the Brazilian strains.

ISOLATION OF *Leptospira icteroides* FROM CASES OF YELLOW FEVER

About the middle of December, it was learned that a disease believed by a local physician to be yellow fever had been prevalent for several weeks in an interior town of about 3,000 inhabitants, Villa Bella das Palmeiras. There was no railroad connection with Bahia, and the journey to Palmeiras required 1 day by steamer, 1 by train, and 4 on horseback. Drs. Vianna and Bião were appointed by Dr. Sebastião Barroso, Chief of the Serviço de Saneamento e Prophylaxia Rural, to make an expedition to Palmeiras. They took with them equipment for making examinations for malarial parasites, reagent for clinical tests for yellow fever, sterile syringes for drawing blood, and 80 hermetically-sealed tubes of leptospira culture medium. The distance and character of the journey made the transportation of experimental animals out of the question.

The medium prepared for the expedition was modified somewhat because of the conditions.[1] The rabbit hemoglobin was omitted, since it undergoes rapid change at ordinary or higher temperatures, and distilled water was substituted for isotonic saline, in order to produce laking of the patient's blood. The tubes were protected from the intense tropical sun by being kept partly submerged in water and covered with green leaves during the journey, both before and after inoculation.

The diagnosis of yellow fever in Palmeiras was confirmed by Drs. Vianna and Bião, and cultures were made from the blood of 1 fatal and 4 non-fatal cases, 6 tubes of medium being inoculated in each instance with quantities of blood in gradually decreasing amounts from 2 cc. to a few drops. The tubes were brought back by Dr. Vianna on Jan. 4, 1924, and were immediately submitted to dark-field examination by several members of the commission. There had been a mould or bacterial invasion in several instances, but the majority of the tubes were free from contamination. A rich growth of the leptospira was found by Dr. Vianna in one of the tubes from Case 3, and somewhat later a positive finding was reported by Dr. Martins in one of the Case 5 tubes. The leptospira was isolated, therefore, in 2 of the 5 cases studied, notwithstanding the unfavorable conditions under which the material had been transported.

Dr. Bião had remained in Palmeiras, and, after Dr. Vianna's departure, made cultures from 4 other cases[2]. The tubes were kept in Palmeiras much longer than the first set, and when Dr. Bião finally reached Bahia with them, most of them were contaminated, and the leptospira could not be detected in any instance.

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[1] A detailed report of the work of the Joint Commission for the Study of Yellow Fever in Brazil has been published as Monograph No. 20 of the Rockefeller Institute for Medical Research, and may be obtained free of charge by application to the International Health Board of the Rockefeller Foundation, 61 Broadway, New York City. For description of culture media, protocols of experimental animals, full histological reports, and illustrations, the reader is referred to the Monograph. The reader is referred also to the separate reports of Dr. Octavio Torres (*Sciencia Medica*, 1924, ii, 219, 313, 394).

[2] The diagnosis in these cases was confirmed by Dr. Elizier Studart.

PATHOGENICITY AND BIOLOGICAL PROPERTIES OF THE BRAZILAN STRAINS OF *Leptospira icteroides*

The original cultures of the Palmeiras strains showed very low virulence for guinea pigs, and were even less pathogenic for marmosets[1]. The guinea pigs used for the inoculations were those of suitable age taken from New York. The Case 3 strain produced fatal infection in only 3 of 8 guinea pigs, and there was almost always a secondary infection with the paratyphoid bacillus in fatal instances. A second passage yielded a greater number of fatal infections. By the third passage, the virulence of the strains for guinea pigs had been increased to such an extent that 0.001 cc. of a mixture of blood and organ suspension, representing both strains, killed guinea pigs in 8 days, that is, the strains had become many thousand times more virulent.

The essential features of the lesions induced by the Palmeiras strains were hemorrhages into the lungs and gastro-intestinal mucosa, nephritis, and fatty degeneration of the liver; jaundice was always present in definite infections. In the milder forms of the disease a febrile reaction, beginning after a period of 4 to 6 days, and persisting 1 day or longer, was the only objective symptom, but positive results were secured by transferring to other guinea pigs blood or suspensions of organs taken during the febrile stage. The demonstration of the leptospira in such materials could rarely be made, and even in the case of very marked infection the leptospira was seldom found. The success of cultivation was also very variable and never readily accomplished.

SUSCEPTIBILITY OF MONKEYS TO THE BRAZILIAN STRAINS OF *Leptospira icteroides*

Macacus rhesus had proved resistant to the strains of *icteroides* isolated from yellow fever in Guayaquil, but the Colombian variety of marmosets had succumbed to infection

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with pronounced symptoms and lesions.[1] The Brazilian marmosets proved unsatisfactory for experiment, being not only relatively insusceptible to *Leptospira icteroides*, but non-resistant to spontaneous bacterial infections. Reproduction of yellow fever was obtained in a striking way, however, in two native monkeys (*Cebus macrocephalus*).

Two African baboons, taken from New York, and 3 Amazon monkeys purchased in Bahia, 2 of the species *Cebus macrocephalus* and 1 black spider monkey (*Ateleus ater*) were inoculated each with 1 cc. of a mixture of rich cultures of the second passage of the Palmeiras strains. The baboons had a rise of temperature for a few days, but otherwise remained well. The spider monkey also had fever on the 3rd day but no other symptoms. Both the *Cebus* monkeys developed typical symptoms of yellow fever after an incubation period of 60 hours. The first febrile period persisted for about 12 hours, there was a brief remission, then a rise to 105.8 to 106° F. on the 4th day, after which the temperature rapidly fell. One of the animals was injected on the 4th day with 15 cc. of anti-*icteroides* immune horse-serum, which had been prepared with the Ecuadorean, Peruvian, and Mexican strains of *icteroides*, and he recovered promptly. The other gradually became weak and listless and refused food — (food taken during the early period of the fever had been vomited). Later he fell to the floor of the cage and seemed delirious, offering slight resistance to handling. Coma developed subsequently, and death occurred 7 days after the first rise of temperature.

The findings at autopsy were typical[2] — faint general jaundice, with distinct yellowness of sclerae and ear lobes; congested gums; yellow, fatty liver; "coffee-ground" stomach contents; melena; subcapsular hemorrhage in the kidney; empty bladder (anuria). Histological study (Dr. Muller)

[1] NOGUCHI, H.; *Journ. Exper. Med., 29:* 585 (June), 1919.

[2] A detailed report of the work of the Joint Commission for the Study of Yellow Fever in Brazil has been published as Monograph No. 20 of the Rockefeller Institute for Medical Research, and may be obtained free of charge by application to the International Health Board of the Rockefeller Foundation, 61 Broadway, New York City. For description of culture media, protocols of experimental animals, full histological reports, and illustrations, the reader is referred to the Monograph. The reader is referred also to the separate reports of Dr. Octavio Torres (*Sciencia Medica*, 1924, ii, 219, 313, 394).

of the organs showed marked fatty infiltration of liver, kidneys, and heart muscle, the fat being present in the form of very fine, closely packed globules. The cells of the convoluted tubules of the kidney were in an advanced stage of cloudy swelling and simple necrosis. Sections of the stomach stained by Perl's Prussian-blue method showed hemosiderin in patches in the surface epithelium, confirming the presence of blood in the "coffee-ground" contents of the stomach.

Suspensions of liver and kidney were negative for the leptospira by dark-field examination, and no growth was obtained on culture medium. Sections of these organs stained by Levaditi's method of silver impregnation revealed no leptospira.

Six guinea pigs simultaneously inoculated with 0.2 cc. of the same culture as controls developed typical symptoms and died in 5 to 7 days.

VIRULENCE OF BRAZILIAN STRAINS FOR YOUNG DOGS

Early in the course of the first transmission experiments of Noguchi[1] in Guayaquil, it had been found that young dogs (6 weeks old) developed typical, and usually fatal yellow fever when inoculated with sufficiently large quantities of virulent material from guinea pigs infected with *Leptospira icteroides*. Later experiments on puppies with strains of *Leptospira icteroides* from Mexico and Peru yielded similar results[2]. The experiments to determine the pathogenicity of the Brazilian strains for young dogs were carried out at the Rockefeller Institute, after the return of the International Health Board Commission from Brazil.

Two pups of a litter about 8 weeks old were inoculated, one intraperitoneally, and the other subcutaneously, each with 5 cc. of a rich culture of Brazilian Strain 5. On the morning of the 7th day after inoculation, one of the animals was found dead, the other was comatose. Both were deeply jaundiced. The second animal died in the afternoon of the same day. At autopsy, "coffee-ground" material was found in the stomach of both animals, and hemorrhages in both stomach and intestines. The livers were pale, and mottled

[1] NOGUCHI, H.; *Journ. Exper. Med., 29:* 585 (June), 1919.

[2] NOGUCHI, H.; *The Lancet, 202:* 1185 (June), 1922.

with lighter-colored patches. The bladder was completely empty in one animal (anuria) and in the other practically so. In one instance the kidneys were large and extensively hemorrhagic, in the other pale. Histopathological study (Dr. Muller) revealed marked fatty infiltration of liver and kidneys. The trabeculae of the liver were distorted; the liver cells were swollen, granular, and vacuolated, and numerous mitotic figures were present; there were hemorrhages and many polymorphonuclears in the sinuses. The kidneys showed marked cloudy swelling and hemorrhages. In the stomach hemorrhages were present in the mucosa and submucosa.

Sections stained by Levaditi's silver-impregnation method revealed the presence of a few fragmented leptospiras in liver and kidney, and the organisms were more numerous in the muscularis of the gastro-intestinal tract.

FILTERABILITY OF THE BRAZILIAN STRAINS

It had already been shown[1, 2, 3] that *Leptospira icteroides* passes through the pores of Berkefeld filters, and it was desirable to demonstrate this property also in the case of Brazilian strains.

A 1 to 100 dilution in isotonic saline of a small quantity of the original culture from Case 5 was divided, and portions were filtered separately through Berkefeld V and N filters. Neither filtrate showed any leptospira by dark-field examination, but growth was obtained in 1 of the 6 tubes of leptospira medium inoculated with the N filtrate, and in 5 of the 6 tubes inoculated with the V filtrate. Definite infection was induced in guinea pigs by inoculation of the cultures obtained from the filtrates.[4]

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[1] NOGUCHI, H.; *Journ. Exper. Med., 30:* 13 (Aug.), 1919.

[2] NICHOLS, H. J.; Personal communication.

[3] DIETERICH, F. H.; *Amer. Journ. Trop. Med.*, in press.

[4] A detailed report of the work of the Joint Commission for the Study of Yellow Fever in Brazil has been published as Monograph No. 20 of the Rockefeller Institute for Medical Research, and may be obtained free of charge by application to the International Health Board of the Rockefeller Foundation, 61 Broadway, New York City. For description of culture media, protocols of experimental animals, full histological reports, and illustrations, the reader is referred to the Monograph. The reader is referred also to the separate reports of Dr. Octavio Torres (*Sciencia Medica*, 1924, ii, 219, 313, 394).

IMMUNOLOGICAL STUDIES — *Pfeiffer Reactions*

A Pfeiffer reaction carried out in April, 1923 [1], with the serum of an American who had had yellow fever in Fortaleza, Ceará, 65 days previously, had indicated that the etiological agent in this case of yellow fever in Brazil was identical with the strains of *Leptospira icteroides* isolated elsewhere. At the time when our work in Bahia was begun, no cases were available for isolation experiments, but an excellent opportunity was offered to test the immunological properties of the sera of persons recovered from yellow fever in relation to the strains of *Leptospira icteroides* obtained from cases of the disease in Ecuador, Mexico, and Peru. Through the coöperation of the physicians who had treated the cases[2], we obtained 9 sera from residents of Bahia, chiefly foreigners, who had had yellow fever during the year 1923. Parallel reactions were carried out with 3 strains of *Leptospira icterohaemorrhagiae*, 2 of American[3], and 1 of Eucadorean[4] origin. The sera of 4 persons who had never had yellow fever were tested simultaneously as controls.

All the sera from yellow fever convalescents gave a positive, and all the normal sera a negative, Pfeiffer reaction with *Leptospira icteroides*, while *Leptospira icterhaemorrhagiae* was entirely unaffected either by the convalescent or the normal sera[5].

As soon as the Palmeiras strains had been isolated, Pfeiffer reactions were carried out with these strains and several of the Bahia convalescent sera. All the Bahia sera gave a clearly positive Pfeiffer reaction with the Palmeiras strains.

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[1] NOGUCHI, H.; *Amer. Journ. Trop. Med., 4:* 131 (March), 1924.

[2] Drs. Fernando Luz, Alberto do Rio, Dias de Moraes, Vidal de Cunha, and Eduardo Araujo.

[3] NOGUCHI, H.; *Journ. Exper. Med., 25:* 755 (May), 1917. WADSWORTH, A., LANGWORTHY, H. V., STEWART F. C., MOORE, A. C., and COLEMAN, M. B.; *Journ. Am. Med. Assn., 78:* 1120 (April), 1922.

[4] NOGUCHI, H.; *Journ. Exper. Med., 30:* 95 (Aug.), 1919.

[5] A detailed report of the work of the Joint Commission for the Study of Yellow Fever in Brazil has been published as Monograph No. 20 of the Rockefeller Institute for Medical Research, and may be obtained free of charge by application to the International Health Board of the Rockefeller Foundation, 61 Broadway, New York City. For description of culture media, protocols of experimental animals, full histological reports, and illustrations, the reader is referred to the Monograph. The reader is referred also to the separate reports of Dr. Octavio Torres (*Sciencia Medica*, 1924, ii, 219, 313, 394).

When Dr. Bião returned from Palmeiras on February 1, he brought back 4 sera from persons who had had yellow fever 2 to 6 weeks previously, 2 of these being from the cases from which the Palmeiras strains had been isolated. All these sera gave a positive reaction with *Leptospira icteroides* from the Ecuadorean, Peruvian, and Mexican sources, as well as with the homologous strains. A specimen of serum obtained a little later from a clinically-clear case of yellow fever occurring in Conceição de Almeida, 2 days journey from Bahia, also gave a positive Pfeiffer reaction with all the *icteroides* strains.

The conclusion is warranted, therefore, that these yellow-fever cases in Brazil were etiologically identical with those occurring in Ecuador, Peru, Mexico, and Colombia[1].

DETERMINATION OF POTENCY OF ANTI-*icteroides* IMMUNE HORSE SERUM

It has already been noted that one of the Brazilian monkeys (*Cebus macrocephalus*) developing typical symptoms of yellow fever following the inoculation of the mixture of the Palmeiras strains, was saved by the administration of anti-*icteroides* serum on the 4th day of illness. The immune serum is that obtained from horses which have been immunized for several years with the various strains (from Guayaquil, Mexico, and Peru) of *Leptospira icteroides*[2]; it had been drawn 2 months previously, transported to Bahia in the refrigerator (4° C.) and kept at about 15° C. after arrival there.

The potency of the serum was tested[3] in guinea pigs infected with a mixture of virulent blood and organ suspension of Palmeiras Strain 3. Each of 10 guinea pigs received a dose representing 1,000 m.l.d., and varying quantities of the immune serum were injected within 30 minutes. The mini-

[1] NOGUCHI, H.; *Amer. Journ. Trop. Med., 4:* 131 (March), 1924.

[2] NOGUCHI, H.; *Journ. Am. Med. Assn., 77:* 181 (July), 1921.

[3] A detailed report of the work of the Joint Commission for the Study of Yellow Fever in Brazil has been published as Monograph No. 20 of the Rockefeller Institute for Medical Research, and may be obtained free of charge by application to the International Health Board of the Rockefeller Foundation, 61 Broadway, New York City. For description of culture media, protocols of experimental animals, full histological reports, and illustrations, the reader is referred to the Monograph. The reader is referred also to the separate reports of Dr. Octavio Torres (*Sciencia Medica,* 1924, ii, 219, 313, 394).

mum quantity of the serum tested (0.0001 cc.) protected guinea pigs against 1,000 m.l.d., that is, 1 cc. of the serum was able to neutralize at least 10,000,000 m.l.d. Experiments in treating infected guinea pigs at various stages of the infection had to be abandoned, because the supply of suitable animals had been exhausted.

SUMMARY

Two strains of *Leptospira icteroides* have been isolated from 2 of 9 cases of yellow fever in Villa Bella das Palmeiras, an interior town in the state of Bahia, Brazil, by inoculation of suitable culture medium with blood drawn on the 1st and 2nd days of illness, respectively.

The characteristic pathogenicity of the Brazilian strains of *Leptospira icteroides* was established by experiments with guinea pigs taken from New York. The initial cultures made with the blood of patients showed a very low virulence for guinea pigs, but by timely passage to fresh animals during the height of fever the virulence of the strains had been increased several thousandfold in the third generation. The essential features of the infection were jaundice, hemorrhages into the lungs and gastro-intestinal mucosa, nephritis, and fatty degeneration of the liver. The leptospira was rarely demonstrable in the materials used for transmission, and the success of cultivation was variable, and never readily accomplished.

Two monkeys of the species *Cebus macrocephalus*, when inoculated with the Brazilian strains of the 2nd passage, developed typical symptoms of severe yellow fever. One recovered after receiving anti-*icteroides* immune serum (horse) on the 4th day of illness; the other died on the 7th day. Autopsy revealed the pathological changes typical of human yellow fever, and histological study of the organs demonstrated the presence of the characteristic fatty degenerative changes of liver and kidney. Three African baboons and a monkey of the species *Ateleus ater*, similarly inoculated, developed slight fever on the 3rd or 4th day, but otherwise remained well.

The Brazilian strains of *Leptospira icteroides* induced in young dogs a fatal infection, characterized by jaundice, hemorrhages (principally into the gastro-intestinal tract, with black vomit) and intense nephritis. Fatty degenera-

tion of liver and kidney was marked. Dark-field examination and cultures were negative, but the leptospira was demonstrated in tissues stained by Levaditi's method of silver impregnation.

The filterability of the Brazilian strains was established by the recovery of the leptospira in culture medium inoculated with Berkefeld V and N filtrates of the original culture of Strain 5. Definite infection was induced in guinea pigs, by inoculation of the cultures obtained from the filtrates.

Sera from 9 persons who had had yellow fever in Bahia 5 to 10 months previously, 4 sera from Palmeiras cases, 2 to 6 weeks after their attack of the disease, and 1 serum taken on the 14th day of illness from a yellow fever patient in Conceição de Almeida, Bahia, all gave positive Pfeiffer reactions when tested with strains of *Leptospira icteroides* from sources in Ecuador, Mexico, and Peru, as well as with the Brazilian strains. Parallel reactions with *Leptospira icterohaemorrhagiae* were uniformly negative. Several normal sera, tested in each instance as controls, gave negative reactions with both organisms. The identity of the yellow fever occurring in Ecuador, Mexico, Peru, Colombia, and Brazil was thus established.

One ten-thousandths of a cubic centimeter (0.0001 cc.) of the anti-*icteroides* serum prepared in horses with strains of *Leptospira icteroides* of Ecuadorean, Mexican, and Peruvian origin protected guinea pigs against 1,000 m.l.d. of a Brazilian strain in the form of a suspension of blood and organs from an infected guinea pig.

HISTOPATHOLOGY AND HEMATOLOGY OF EXPERIMENTAL YELLOW FEVER*

HENRY R. MULLER, M.D.

The guinea pigs used in the experiments to be reported here weighed about 200 to 300 grams, experience having shown that larger animals are only slightly or not at all susceptible to experimental yellow fever. Likewise in the case of dogs, it was necessary to use puppies 6 to 8 weeks old.

In order that the material obtained from animals might be comparable with *post mortem* material from cases of human yellow fever, the disease was allowed to run its natural course to death, whenever practicable, or the animals were killed while moribund. Care was taken, also, to avoid infecting the animals in an unbroken series of passages, the infection being induced by cultures of *Leptospira icteroides*, so far as possible. Noguchi has pointed out[1] that:

> Guinea pigs and dogs in an unbroken series of passages become less jaundiced, the liver is less fatty, the kidneys and other tissues are more hemorrhagic, and finally death occurs with a veritable leptospiremia. The picture in such animals is quite unlike that in animals inoculated with a strain freshly isolated from human cases, or one passed through a few generations on the leptospira medium after passage through animals. Under natural conditions *Leptospira icteroides* never passes directly from man to man, but only, so far as we know, through the medium of the mosquito, *Ædes ægypti*, in the body of which it remains for many days as though in culture; hence its characteristic pathogenicity is maintained. If yellow fever were trans-

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*The gross and histological changes described in this article are illustrated in the colored plates incorporated in Monograph No. 20 of the Rockefeller Institute for Medical Research, published in August, 1924. The reader is referred also to the reports of Dr. Octavio Torres. *Sciencia Medica*, 1924, vol. II, pp. 219, 313, 394.

[1] NOGUCHI, H.; "Researches on Yellow Fever. Comparative Etiological, Pathological, and Epidemiological Considerations: Prevention and Treatment." *The Lancet*, 1922, ccii, 1185.

mitted directly from man to man in an unbroken series of passages, the clinical picture might be a different one.

Failure to avoid a long series of passages and to allow the infection to run a natural course may partly explain why Wanstrom[1] did not find marked fatty degeneration of liver and kidney. W. H. Hoffmann,[2] who also obtained unusual results, used guinea pigs which were in the 20th to the 50th passages of a long series of infections with a strain passed from animal to animal.

HISTOPATHOLOGICAL CHANGES INDUCED IN GUINEA PIGS BY THE EXPERIMENTAL INFECTION

Liver. — In general, it has been found that in guinea pigs inoculated with *Leptospira icteroides*, in which the infection has been allowed to run a natural fatal course, the liver is paler than normal and looks in the gross like a fatty liver. Microscopically, the normal structure is seen to be greatly disturbed, the trabeculae being distorted, and the sinuses compressed. The liver-cells are slightly separated from one another, so that the cells present a loose texture. The cells are swollen and granular and have numerous fine, round, and irregular vacuoles. Irregularly scattered throughout the section are numerous small groups of cells, with indistinct outlines and with nuclei in various stages of karyolysis or karyorrhexis, or entirely without nuclei. Associated with these necrobiotic changes, numerous mitotic figures are constantly found. All phases of normal cell-division are encountered, showing that active regeneration of liver-cells is taking place, following the death of cells.

Fatty infiltration of the liver of these guinea pigs is a very constant finding, as is brought out by Scarlet R or Sudan III. It may be very severe, involving almost the entire lobule; or it may be less marked, and limited to the periphery of the lobule; or it may be scattered diffusely throughout the lobule in small foci.

Small foci of hemorrhages may be present. Polynuclear leucocytes are sometimes encountered among the swollen

[1] WANSTROM, RUTH C., "Occurrence and Staining of *Leptospira icteroides* in Guinea Pigs Inoculated Experimentally, with a Study of the Lesions Produced." *Journ. Infect. Dis.*, 1924, xxxiv, 110.

[2] HOFFMANN, W. H., "The Histopathology and Haematology of Guinea Pigs Infected with *Leptospira icteroides*." *Journ. Trop. Med. and Hyg.*, 1922, xxv, 353.

liver-cells, apparently lying in the compressed sinuses, and there is often a round-cell infiltration of the periportal connective tissue.

Kidneys. — In most cases the epithelium is greatly swollen, so that the lumen of the convoluted tubules is either completely obliterated or filled with pink-staining granular material. Hyalin and granular casts are frequent. The cytoplasm is granular and finely vacuolated. Frequently the degenerative processes in the cells have gone on to complete necrosis, so that individual cells or most of the cells of a tubule are without nuclei or have nuclei in various stages of karyorrhexis or karyolysis. In a large percentage of instances, mitotic figures are present, showing that repair of the damage is taking place. Mitotic figures are generally not found in tissues of animals dying before the 5th day of disease.

Fatty infiltration, usually not quite so severe, nor quite so constantly present as in the liver, is found in the cells of either the convoluted or the collecting tubules, or in both. Minute hemorrhages in the cortex and medulla, or hemorrhages into lumen of tubules, or larger hemorrhages beneath the capsules, may be present. Congestion of the glomeruli may also appear. Cellular infiltration is rare in the interstitial tissue and is never found in the glomeruli.

Heart. — Petechial hemorrhages into the papillary muscles and sub-endocardial and subepicardial are frequently observed. Zenker's degeneration was never seen, notwithstanding careful search for it.

Fatty infiltration usually occurs in patches; it is present in a large number of instances, but not so constantly as in either the liver or the kidney.

Lungs. — Corresponding with the hemorrhagic spots seen in the gross, the sections show foci in which hemorrhage has occurred into a number of adjacent alveoli.

Gastro-intestinal Tract. — In the mucosa of the stomach are hemorrhages, sometimes quite extensive, corresponding with those that are uniformly seen in the gross. Hemorrhages often occur in the mucosa of the colon.

Spleen. — As would be expected from the practically unchanged appearance of the spleen in the gross, the microscopic sections present only rarely very slight changes. In

some cases there may be a moderate or a very slight diffuse polynuclear infiltration. Occasionally the sinuses are slightly dilated. Only in a few instances is there a phagocytosis of red cells. The lymph follicles are not changed. Pigment is rarely found.

Lymph Nodes. — The lymph nodes, such as those of the mesentery, very rarely are enlarged, and the lymph follicles and Peyer's patches of the intestines are never involved in cases which are free from secondary infection, such as paratyphoid.

The lesions found in guinea pigs[1] are illustrated by the following protocols of animals inoculated with the Brazilian strains of *Leptospira icteroides.*

Guinea Pig XXII – 46. — Inoculated March 22, 1924, with 0.5 cc. of culture of Brazilian Strain 3. March 24, temp. 104.8°F. (40.5°C.). March 25, temp. 105.2°F. (40.7°C.). March 26, temp. 103.8°F. (39.9°C.); blood obtained by heart puncture showed one leptospira after 5 minutes' search with the dark-field microscope. March 27, temp. 104.6°F. (40.7°C.). March 28, temp. 103.6°F. (39.8°C.). March 29, animal markedly jaundiced; temp. 101°F. (38°C.); moribund; killed.

Autopsy. — Marked general jaundice; hemorrhages of skin and subcutaneous tissues. Stomach contained black and blood-stained particles; hemorrhages in the mucosa of the stomach, in the lungs, and a few in the capsules of the kidneys. One leptospira found by dark-field examination in kidney suspension, but none in either citrated heart-blood or liver suspension. Cultures of spleen in broth and on plain agar remained sterile.

Liver. — Parenchyma cells slightly separated from one another, and are swollen so that the sinuses are almost all obliterated. Cytoplasm granular, pink-staining, and finely vacuolated. Some nuclei are fragmented; no mitotic figures found. Around the structures of the portal canals is an infiltration of large mononuclears, with a few lymphocytes and polynuclears. A few polymorphonuclears and lymphocytes are scattered among the liver-cells. Staining

[1] The tissues in all cases were fixed in formalin and stained with hematoxylin and eosin; when fat was to be demonstrated, they were stained with Scarlet R or Sudan III.

with Scarlet R reveals numerous fine fat-droplets in the liver cells occupying the central half of the lobule. Levaditi sections fail to show the leptospira.

Kidneys. — Swelling of the epithelium of the convoluted tubules is so marked that the lumen is obliterated. Cells granular and finely vacuolated. A few minute hemorrhages are present between the tubules and within their lumens. With Scarlet R a marked fatty infiltration of the epithelium of the collecting tubules can be demonstrated. Levaditi sections reveal numerous leptospira in the cortex of the kidney, outside the tubules, as well as within the epithelial cells.

Heart. — Minute hemorrhages are present. Around the small blood-vessels are collections of large mononuclears and a few polymorphonuclears. In Scarlet R sections, patches of muscle-fibres are seen to contain numerous fine drops of fat.

Stomach. — Extensive hemorrhages into mucosa and between muscularis mucosae and muscularis are present. There are patches of necrotic mucosa, sharply demarcated from the rest, and surrounded by a zone of polynuclears at the base and extremities. The surface of the necrotic patch contains brown blood-pigment.

Intestines. — Peyer's patches not enlarged; hemorrhages present in mucosa of large intestine.

Guinea Pig XXII – 72 – A. — Weight 200 grams. Inoculated April 7, 1924, with 1 cc. citrated heart-blood from infected guinea pig 68 B, which had been inoculated with blood from guinea pig 57 A; the latter had received 0.5 cc. culture of *Leptospira icteroides*, Brazilian Strain 5. April 12 and 13, temp. 104°F. (40°C.). April 14, temp. 102.2°F. (39.°C.); blood obtained by heart-puncture contained 4 leptospira in 150 fields, and cultures made with the blood showed marked growth of *Leptospira icteroides* on April 22; cultures on broth and agar remained sterile. April 15, animal died.

Autopsy. — Jaundice; hemorrhages into subcutaneous tissues; hemorrhagic spots in lungs; hemorrhages around both kidneys; one large hemorrhagic spot in stomach, near cardia, and several small spots on external wall of stomach

and intestines; liver is light brown and friable; spleen is normal.

Liver.— The liver-cells, which are large and polyhedral, have a tendency to be separated from one another. The cytoplasm is granular and finely vacuolated. A few scattered cells are conspicuous because they stain more deeply red. Most of the nuclei are spherical and appear normal, but there are many undergoing mitotic division. In the periportal connective tissue there is an infiltration of large mononuclears and a few lymphocytes and polynuclears. In Scarlet R sections, the liver-cells are found to contain fat-droplets. Nearly the entire lobule is involved, but a narrow zone on the periphery of each lobule is less affected. In Levaditi sections, the leptospiras are found in large numbers, uniformly scattered, lying chiefly between, but also within, the liver cells.

Kidneys. — The cells of the convoluted tubules are swollen, granular, and vacuolated. The lumen in some places is nearly obliterated by the swollen epithelium. Many tubules, both convoluted and collecting, contain red blood cells, others pink-staining, finely-granular débris and casts. Small hemorrhages are present in the interstitial tissue. The glomeruli are slightly congested. Scarlet R brings out small foci of fat in the epithelium of the collecting tubules. In Levaditi sections, a rather large number of leptospiras are found, chiefly between the tubules, but also within the kidney-cells.

Heart. — In the papillary muscles and beneath the endothelium are found minute hemorrhages, in the vicinity of which are polynuclears and large mononuclears. Scarlet R sections show that numerous patches of muscle-fibres contain many fine drops of fat. Levaditi sections reveal a few isolated leptospiras in the muscle-fibres.

Stomach. — Numerous and extensive hemorrhages are present in the mucosa and muscularis.

Intestines. — Peyer's patches normal. Hemorrhages present in mucosa of colon.

Spleen. — Normal.

Skeletal muscles. — No Zenker's degeneration; a few petechial hemorrhages in abdominal muscles.

HISTOPATHOLOGICAL CHANGES INDUCED IN DOGS BY THE EXPERIMENTAL INFECTION

The following descriptions are based on histopathological study of the tissues of 2 puppies, of a litter about 8 weeks old, which were inoculated with a rich culture of *Leptospira icteroides*, Brazilian Strain 5, each receiving 5 cc., one subcutaneously and the other intraperitoneally. On the 7th day after inoculation, both dogs died, and autopsy revealed deep jaundice; "coffee-ground" material in the stomach; pale, soft livers; pale kidneys in one, and hemorrhagic kidneys in the other animal. Both had very few hemorrhages in the skeletal muscles. In one instance, there was no urine in the bladder; but the bladder of the other animal contained 2 or 3 drops of highly albuminous urine, as shown by Heller's test.

Liver. — In young dogs the changes in the liver are more striking than in guinea pigs. There is evident very severe disturbance, so that the trabeculae can scarcely be distinguished. The trabecular arrangement of cells is lost; the individual cells are swollen, granular, vacuolated, and slightly separated from one another. There are minute foci of cells without nuclei, or with nuclei which are pale and indistinct. Great variations appear in the staining quality of the nuclei. Mitotic figures, which point to an extensive reparative process in the liver, are frequently encountered. In the compressed sinuses are many polynuclears. Congestion and hemorrhage are present, and in one puppy the liver is the seat of large, round cells stuffed with erythrocytes. The liver of one dog, as shown by staining with Scarlet R, presents fatty infiltration of the entire lobule; in the other animal the fat is in the central and intermediate zones. There are also droplets of fat in the epithelium of the bile ducts.

Kidneys.—In the kidneys of one animal, there are complete necrosis of the epithelium and extensive hemorrhages into the tubules, interstitial tissue, and glomeruli. In the other animal, the cells of the convoluted tubules are swollen and granular, and the lumen of the tubules is occluded by swollen cells. Many cells are without nuclei (indicating death of cells) and in many others mitotic figures are present, pointing to a reparative process. The urinary bladder is normal in both animals.

The kidneys in both instances have marked fatty infiltration of the collecting tubules, as is brought out with Scarlet R. In addition, the kidneys showing extensive hemorrhages have also fatty infiltration of the endothelium of the glomeruli.

Heart. — Both puppies show (1) an infiltration of fat in the muscle-fibres, in the form of fine droplets, and (2) a few petechial hemorrhages. Zenker's degeneration absent.

Lungs. — There are a very few small foci of hemorrhages into the alveoli. They are very much fewer in number than those found in guinea pigs.

Spleen. — In one animal the spleen is practically normal; in the other, it is slightly congested and has a few phagocytes filled with red blood cells.

Mesenteric lymph nodes. — A moderate number of erythrophagocytes are present.

Pancreas. — There is a very marked interstitial infiltration of polynuclears in both animals. A few minute hemorrhages exist in the interstitial tissue of one animal.

Stomach. — Hemorrhages, rather extensive, are found in the submucosa, and congested vessels and small hemorrhages are present in the mucosa.

Intestines. — Peyer's patches uninvolved.

Skeletal muscles. — The abdominal muscles are the seat of minute hemorrhages, but no degeneration of the muscle-fibres is present. The hemorrhages in the skeletal muscles are very much less numerous and extensive than in guinea pigs.

Levaditi sections. — The leptospira could be demonstrated in varying numbers in practically all the organs — liver, kidneys, heart, lung, spleen, intestinal wall, pancreas, lymph nodes, and skeletal muscles. Many of the organisms were fragmented forms.

HISTOPATHOLOGICAL CHANGES IN EXPERIMENTALLY INFECTED MONKEYS

The tissues examined were obtained from one of 2 animals of the species *Cebus macrocephalus* which had been inoculated with mixtures of cultures of Brazilian Strains 3 and 5. The first rise of temperature occurred 60 hours after inoculation. The animal died on the 7th day after onset of fever.

Liver. — In the hematoxylin and eosin sections the liver

trabeculae are distinct, and the liver-cells are large, polyhedral, and vacuolated. The vacuoles are variable in size, and there are 6 to 10 in each cell. The closely packed vacuoles make the cytoplasm appear reticulated. The nuclei are large and round, and most of them lie towards the centre of the cells. The blood-sinuses are dilated, and filled with blood. The blood-vessels and bile-ducts of the portal canals are normal.

In Scarlet R sections, the fat globules fill almost the entire liver cell, and every lobule, except for a narrow zone around the central vein, is completely fatty. Towards the periphery of the lobule, the fat-globules tend to be larger and conglomerate. The epithelium of the bile-ducts shows no fatty change.

Kidneys. — In the hematoxylin and eosin sections, the cells of the convoluted tubules have indistinct outlines and appear as pink-staining, granular, and vacuolated masses almost completely occluding the lumen. The nuclei are smaller than normal, and pyknotic. Minute hemorrhages are present in the medulla of the kidney. The glomeruli are normal.

In Scarlet R sections, the cells of the convoluted and collecting tubules contain numerous closely packed fine fat-droplets, situated mainly at the base of the cell. This fatty infiltration is very marked.

Heart. — There are no hemorrhages nor any form of degeneration, such as Zenker's. In Scarlet R sections, numerous fine fat-droplets are uniformly sprinkled throughout the entire length of all the muscle-fibres.

Lungs. — The alveoli are free from exudate, but there is a slight degree of chronic, productive, inflammatory tissue around the bronchioles.

Stomach. — The mucosa presents extensive *post mortem* change. There are defects in the mucosa, which extend part or all of the way to the *muscularis mucosae*, and these are filled with dark-brown, coarse and fine granules of blood-pigment. The cells lining the edges of the defects contain pigment in the cytoplasm. By Perl's Prussian-blue method for demonstrating hemosiderin (derived from the hemoglobin of red-blood corpuscles) the pigment stains blue, where it is in contact with the epithelium, and the mucosal defects also have blue linings. The presence of blood in the "coffee-ground" material in the stomach is thus evident.

Intestines.—Peyer's patches uninvolved. Mucosa normal. *Spleen, adrenal, pancreas,* and *large intestine* are all negative.

Levaditi sections fail to reveal leptospira in any of the organs; in view of the fact, however, that Leptospira can rarely be demonstrated in human autopsy material, this negative finding is not remarkable.

HEMATOLOGICAL STUDIES OF EXPERIMENTALLY INFECTED GUINEA PIGS

As preliminary to a study of the blood-changes in guinea pigs experimentally infected with yellow fever, a record was kept of the blood-counts and hemoglobin estimates of a large number of normal guinea pigs (250 to 300 grams) such as are used for transmission-experiments in yellow fever. The blood was obtained by puncturing the ear veins.

The average number of leucocytes in 60 normal animals was 8,365 per cubic millimeter. Of the 60 animals, 13 had total leucocyte counts of over 10,000, and 9 had counts under 5,000. The highest count on any one animal was 23,500, and the lowest 4,120 per c.mm. There appear, therefore, to be wide variations in the normal white-counts and the unusually high counts (above 10,000) seemed to be peculiar to certain apparently quite normal animals. It was interesting to find that, in some instances, animals of the same litter all had high normal counts, — as, for example, the following in a litter of four: 14,400; 16,700; 23,500; 12,800.

The average total red-blood-cell count in 50 normal guinea pigs was found to be 5,480,440 per c.mm. The highest individual count was 6,930,000, and the lowest 4,340,000.

The hemoglobin estimates were made by the Tallquist method. The average percentage in 33 normal animals was 80. (Later it was found that much higher readings are obtained by the Sahli method — between 100 and 110%).

Guinea pigs which were inoculated with virulent cultures of *Leptospira icteroides,* and of which blood counts were made, may be divided into 3 groups: (1) those which had fatal infections; (2) those which had infections, but which were killed before the natural termination of the disease; and (3) those which passed through infections and recovered.

As indicated in Table 1, 5 guinea pigs were inoculated with a mixture of cultures of *Leptospira icteroides* (Guayaquil and

Peruvian strains) with citrated blood from a guinea pig infected with the Guayaquil strain of *L. icteroides*. The course of the infection was typical in each instance, and 3 of the animals died on the 8th, 9th, and 11th days, respectively, after inoculation. The autopsy findings were typical and uncomplicated.

BLOOD COUNTS ON GUINEA PIGS FATALLY INFECTED WITH L. ICTEROIDES

	Guinea Pig XX-92A 0.01 c.c. Virus (Arias + Vilela)		Guinea Pig XX-92B 0.01 c.c. Virus (Arias + Vilela)		Guinea Pig XX-93B 0.1 c.c. Virus (Arias + Vilela)		Guinea Pig XX-94A 1.0 c.c. Virus (Arias + Vilela)		Guinea Pig XX-94B 1.0 c.c. Virus (Arias + Vilela)	
	Temp & Icterus	Blood Counts	Temp & Icterus	Blood Counts	Temp & Icterus	Blood Counts	Temp & Icterus	Blood Counts	Temp & Icterus	Blood Counts
Before Inoculation		9,260 4,560,000		7,700 5,820,000		5,850 4,590,000		7,500 6,000,000		7,950 4,620,000
1st day after inoculation										
2nd " " "		12,200		8,050		6,400 5,350,000		6,750		6,900
3rd " " "										
4th " " "	105.6°	9,640	104.4°	9,280	106°	3,150	104.4°	5,600	103°	8,000
5th " " "	104.4°		105.4°		105.2°		103.4°		104.4°	
6th " " "	101.8°	8,700 4,800,000	102.8°	5,400 5,270,000	101.9°	3,520 4,440,000	102°	5,300 4,720,000	101.6°	5,000 4,680,000
7th " " "	104.6°		100.2°		103°	70% Jaundice	102.4°	9,400 3,340,000 60% Jaundice	102°	
8th " " "	102.6°		102.6°		100.6°		Died Autopsy, Typical		99°	
9th " " "	Died Autopsy, Typical		Died Autopsy, Typical		98°	No blood obtainable from ear for count			Died Autopsy, Typical	
10th " " "					95°					
11th " " "					Died Autopsy, Typical					

Table 1

On 2nd day after inoculation, 2 of the 5 animals showed a slight drop in the leucocyte-count, from 7,500 to 6,750, and from 7,950 to 6,900, respectively. Of the other 3, 2 had only slight rises in total counts on the second day after inoculation, so slight that they may be disregarded (from 7,700 to 8,050, and from 5,850 to 6,400, respectively). In one animal only was there an increase, from 9,260 to 12,200. During the course of fever the leucocyte-counts gradually fell in each instance, to slightly below normal, the largest drop being one of 40%, which occurred on the 6th day after inoculation, in the animal which died on the 11th day of the disease. In this pig, no blood was obtainable from the ear on the 9th day; hence no further counts were made.

In one instance, that of the animal which died on the 8th

BLOOD COUNTS ON GUINEA PIGS INFECTED WITH L. ICTEROIDES AND WHICH WERE KILLED

	Guinea Pig XX-119A 0.1 c.c. Arias Culture		Guinea Pig XX-119B 0.1 c.c. Arias Culture		Guinea Pig XX-120A 1.0 c.c. Arias Culture		Guinea Pig XX-120B 1.0 c.c. Arias Culture		Guinea Pig XXI-117A 0.4 c.c. Arias Culture	
	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts
Before Inoculation		16,700 5,570,000 80% Tall.		23,500 4,820,000 70%		12,800 4,730,000 90%		20,000 4,500,000 90%		13,720
1st day after inoculation	101.6°	15,000 80% Tall.	100.6°	19,100 75%	101.2°	9,680 5,066,000 90%	102°	14,000 5,000,000 90%	104.2°	11,565
2nd " "	101.9°	13,200 5,160,000 90%	101.8°	15,000 4,520,000 80%	101.4°	8,900 4,900,000 80%	101.2°	11,050 5,008,000 85%	104°	
3rd " "	103.4°		103.8°		102°		103.4°			8,200
4th " " "	102.4°	13,900 4,900,000 75%	105.4°	23,030 5,520,000 80%	104.8°	13,000 5,500,000 80%	104.4°	15,200 5,500,000 75%	104.6°	
5th " " "	105.2°	11,000 5,300,000 80%	104° ++ KILLED	19,700 3,400,000* 65%	104°	12,500 4,810,000 85%	101.2° ++	14,000	105.2°	4,365
6th " " "			AUTOPSY TYPICAL LEPTOSPIRA IN BLOOD		103.4°		98° ++ KILLED		103.8° +	7,800
7th " " "	102.8°		* BLED FROM HEART		104.8°	18,800 5,200,000 85%	AUTOPSY TYPICAL LEPTOSPIRA IN BLOOD & LIVER EMULSION		104° ++	10,480 4,300,000 70%
8th " " "	102° ++ KILLED				103.6° ++ KILLED				101.8° +++ KILLED	7,720 4,700,000 65%
9th " " "	AUTOPSY TYPICAL LEPTOSPIRA IN BLOOD LEVADITI SECTIONS +				AUTOPSY TYPICAL NO LEPTOSPIRA IN BLOOD LEVADITI SECTIONS —				AUTOPSY TYPICAL NO LEPTOSPIRA IN KIDNEY OR LIVER EMULSIONS	

Table 2

day, a count made on the day before death showed a rise to 9,400 from the animal's normal count of 7,500.

Red-cell counts made on these 5 animals, on the 6th day after inoculation, showed practically no change from the normal, except in the animal which died on the 8th day, in which a reduction of red cells to 4,720,000 and 3,340,000 took place on the 6th and 7th days, respectively. This pig gave a reading of 60% hemoglobin by the Tallquist method on the 7th day. Unfortunately, only one other hemoglobin estimate was made on this series of animals, on the 7th day in the guinea pig which died on the 11th day; the percentage was then 70%.

Of 5 guinea pigs which were typically infected with variable quantities of culture of *L. icteroides* (Guayaquil strain) and were killed between the 5th and 9th days after inoculation (Table 2), all showed a gradual reduction in the total number of leucocytes on the 1st and 2nd days after inoculation. This reduction continued, with some slight fluctuations, and the count remained well under the initial normal one except in one instance, — in which, on the 7th day after inoculation, the leucocytes rose 47% above the normal. In 4 of 5 animals the red cells remained close to normal —

or even, during the course of the fever, showed a slight numerical increase.

The hemoglobin likewise showed very slight changes from the normal.

There were 3 guinea pigs in which infection occurred following the inoculation of *L. icteroides* culture, and in which recovery took place (Table 3). Although all of

BLOOD COUNTS ON GUINEA PIGS INFECTED WITH L. ICTEROIDES AND WHICH RECOVERED.

	Guinea Pig XX-93A. 0.1 cc. virus. (Carbon + Vaccine)		Guinea Pig XXI-116A 0.4 cc. Agar Culture		Guinea Pig XXI-123B 1 cc. Vaccine Culture	
	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts	Temp. & Icterus	Blood Counts
Before Inoculation		15,600 4,640,000		7,800		4,040
1st day after inoculation		16,000	103.4°	9,800	103°	11,960
2d " "		18,400 5,340,000	102.5°		101.5°	
3d " "				8,280	101.5°	4,940
4th " "	106.4°	10,700	104°		104.5°	
5th " "	104.2°		104.2°	9,200	104.6°	6,560
6th " "	104°	7,720 4,670,000	104.4° ±	11,200	103°	8,140
7th " "	104°	12,200 4,033,000 70% Lab	105°	8,660 5,418,000	105.6°	9,920 6,580,000 75%
8th " "	104.3°		103.2° +	9,280 4,660,000 70%	103.4°	
9th " "	100.5°	15,660 4,670,000 50%	103.5°		102.8°	"
10th " "	100.2°		102.		101.5°	
11th " "	102.5°		101.8°		102°	
12th " "	101.8°					
13th " "	101°	14,600 4,940,000 80%				
14th " "	102.8°					

Table 3

these animals ran a typical course of fever lasting 3 to 5 days, but one was jaundiced, and only slightly. In one animal of this series, the number of leucocytes remained stationary during the first 24 hours after inoculation (15,600–16,000). In another the count was slightly increased after 24 hours (7,800 to 9,800), and in the 3rd there was a marked increase (from 4,040 to 11,960). Both these animals had a leucocyte-count very slightly above the normal throughout the course of fever, while in the 1st

animal the leucocyte-counts remained low during the febrile period, and gradually returned to normal on the 9th day after inoculation (first afebrile day of convalescence).

The red-cell count in the first guinea pig remained at, or slightly above, normal throughout the period of fever, and on the 1st and 5th days of convalescence. Its hemoglobin, however, dropped from 70% (on the 4th day of fever) to 50% (on the first afebrile day). In the 2nd animal the number of red cells dropped slightly on the first afebrile day, and its hemoglobin on that day was 70%.

SUMMARY

In young guinea pigs, young puppies, and in a monkey (*Cebus macrocephalus*) experimentally infected with yellow fever, the histological changes, although varying in degree, are similar to those found in human cases.

In experimental yellow fever in guinea pigs a steady and persistent leucopenia of moderate degree, during the course of severe infections, is the rule. In occasional instances, an initial or a preagonic leucocytosis may be present. In extremely mild infections there may be a slight leucopenia. or a mild leucocytosis during the febrile period, according to the individual case.

The number of red cells usually remained within normal limits, although a marked reduction occasionally took place, and in some instances there was even a slight increase.

The hemoglobin was generally normal. In some animals, it was a trifle below the normal.

These findings are similar to those of yellow fever in man, as recorded in the literature.

THE RESULTS OF THE NOGUCHI TREATMENT AND THE PROPHYLACTIC MEASURES EMPLOYED IN THE 1921 YELLOW-FEVER EPIDEMIC IN BELIZE

James Cran, M.D.

In 1921, in Belize, there occurred an outbreak of yellow fever, which is of interest in that the Noguchi Serum and Vaccine were extensively used, and accurate records were kept.

The outbreak occurred about a mile from the outskirts of the town, in a large secondary college in the lee of the prevailing breezes.

The pupils consisted of upward of 100 day scholars from Belize, and a similar number of boarders from the neighboring Republics of San Salvador, Guatemala, Mexico, and Honduras. In the 3 former countries, cases of yellow fever were known to have occurred within the previous 12 months.

Nearly all the boarders returned by sea to the College in the month of July, after the summer vacation, and there can be little doubt that an ambulatory case of yellow fever returned amongst them.

That Belize has been so free from yellow fever in past years, in spite of its propinquity to, and daily intercourse with, infected countries is probably due to its rigid enforcement of passenger inspection.

Owing, however, to the number of arrivals at the College, and the distance from the reporting station (over two miles), permission was given to the Infirmarian, an intelligent and experienced man, to take the temperatures and report any above normal. Inasmuch as this officer was one of the early victims himself, his statement could not be taken, but it is likely that there might have been a case which he failed to notice, or which was so similar to those he was in the habit of treating as malaria, that his suspicions were not aroused as to the possibility of its being anything else. However, on August 18, the College physician was called, and on the following morning he reported his suspicions to the health

authorities. The Principal Medical Officer on arrival at the College found three well-marked cases of yellow fever, one in its 6th day, moribund, and each of the other two in its 5th day.

The Infirmarian himself had been sick for 4 days, although still performing his duties; and his clinical symptoms were not so definite, as he was suffering from chronic malaria and nephritis. In addition, 3 other cases were also found, a total of 7. All were immediately given Noguchi Serum intravenously, of which fortunately there was a supply on hand. The 4 cases receiving treatment in the late stages of the disease, died; the 3 receiving the serum in the earlier stages, recovered.

Vigorous measures were at once taken by the authorities. The school was placed under strict quarantine; and a medical officer was established in residence, with a competent staff.

Next day every inmate, except those actually suffering from the disease, was inoculated with Noguchi Vaccine, and subsequently all the day scholars were inspected twice daily for six days. None of the latter contracted the disease. The fact that they used the buildings only when the sun was at its hottest, may have had some bearing on this.

All of the buildings were fumigated, so far as possible, with 2 pounds of sulphur to 1,000 cubic feet. It was, however, impossible to make this thorough, as the fumigation had to be done in sections, the inmates, 150 in all, being moved from one building to another as required.

Within 5 days after this fumigation, 7 more cases occurred. During the next 7 days there were no further developments, and it was hoped that all the infected mosquitoes had been destroyed, or that the vaccinations were thoroughly preventive, or both. Unfortunately this hope proved ungrounded, as on September 2 (or 7 days after the fumigation) 2 more cases occurred, and another on the following day. It was thus evident that infected mosquitoes were still present. The authorities thereupon determined to take drastic action, which, although unpopular at the time, has since been admitted by all to have been wise.

I cannot do better than quote the description of these measures as reported by Dr. Gann, the Principal Medical Officer:

It was then realized that the only means of putting an effectual stop to the disease was the removal of all the inmates of the College to a place where no Stegomyia existed, and a fumigation of the College and its outbuildings during their absence, so thorough as to render it practically impossible for any infected mosquito to survive. The College Authorities were very much opposed to any such complete removal of all the boys and the staff from the College Building, in Loyola Park, and it became necessary for the Local Board of Health to serve a notice on them, to the effect that under the Public Health Ordinance such a removal would be compulsory.

The site chosen for the segregation of the inmates of the College was a small sandy island named Sergeant's Cay, situated about 12 miles from Belize, where, after careful inspection by the government medical officers, and by the representative of the United States Public Health Service then in Belize, it was ascertained that no Stegomyia mosquitoes were to be found. This Cay had the further advantage of having an ample supply of vat-stored water and four good houses with cooking accommodations.

The Cay was acquired by the Government for the purpose. The housing accommodations were supplemented by the erection of wood-floored tents and a marquee, together with the provision of ample latrine accommodations and cooking facilities. Those preparations took time, and it was not till September 13 that the boys were removed to Sergeant's Cay. They remained there till the 23rd, under the supervision of Dr. Folse, Assistant Medical Officer, who lived on the Cay; and all enjoyed excellent health. No case of yellow fever developed amongst either the boys or the staff. On the 23rd some of the boys returned to their homes, while those who lived in Guatemala and Spanish Honduras were shipped off to those countries, though the boat which took the Honduran boys to Puerto Cortez was refused *pratique* by the Port Authorities, and they were shipped back to Belize without being allowed to land, or the vessel's even being permitted to procure provisions or water.

Between the 13th and the 23rd the College, with its outbuildings, was twice most thoroughly fumigated with sulphur; the cracks in the windows and doors were securely pasted over with paper, while all the larger openings were closed by having tarpaulins, ground sheets, and blankets nailed over them, so that it would have been impossible for any mosquito within the building to escape. In the open space beneath the main building, and in the extensive verandas which run all around it, pots of sulphur were burnt before the fumigation proper took place,

in order, as far as possible, to drive the mosquitoes haunting these situations to the interior of the buildings, where they would be killed by the fumigation.

On the 5th of October, Loyola Park was declared to be no longer an infected place, under the Public Health Ordinance, and it was reoccupied. As no further case of yellow fever has occurred there since, it may, I think, be accepted that no infected mosquito escaped the double fumigation, and that the precaution taken in isolating the whole community for ten days on Sergeant's Cay, and thoroughly fumigating the College during their absence, had been successful, so far as the College was concerned, in ending the epidemic.

The outbreak had thus far proved the value of the Noguchi Serum as a curative agent, but left that of the Noguchi Vaccine in doubt. The efficacy of the latter, however, appears to me to have been demonstrated by the further history of the outbreak, which later on reached the town.

Immediately after the outbreak occurred at the College, free vaccination for all was instituted at the Public Hospital; and with a few exceptions that part of the population commonly regarded as non-immune gladly availed themselves of it, but comparatively few of the natives did so. More than 500 were vaccinated, and of this number at least 150 may be regarded as having been newcomers.

After an interval of 3 weeks, a negro laborer living in the heart of the town was admitted to the Hospital on September 27. He gave a history of having been taken ill with fever on the 18th, and of having had complete suppression of urine since the 22nd. Yellow fever was diagnosed, and he was given the Noguchi Serum on the 10th day of the disease. He died on the 12th day of the disease, having had almost complete suppression for 7 days, only a few c. c's of a bloody fluid having been drawn off. He had not received a prophylactic.

There were only 2 more cases in this outbreak, and although neither of them occurred in Belize, yet both of them must have received their infection there.

A young white woman who had resided in Belize for a few months, left the colony for New Orleans on November 5. On the following day she developed fever, which was diagnosed as malaria. When she arrived in New Orleans, on the 8th, she had no temperature and was allowed to land. Shortly after landing, she again developed a temperature,

which on the 10th was diagnosed as yellow fever. She died almost immediately afterward and this diagnosis was confirmed at the autopsy, on the 11th. This woman was one of the few newcomers who had persistently refused to be vaccinated, being prejudiced against it because she believed that an aged relative had died in Rome after receiving what seemed to be a similar injection, for pneumonia.

On October 31 a young man arrived in Belize from Mobile, Alabama. He remained for 12 days, and then proceeded to a coast town about 40 miles distant. Next day he developed yellow fever. On the 4th day of the disease he received 60 c. c. of Noguchi Serum, and made an uneventful recovery.

If it be only a coincidence, it seems a strange one, that the only two whites who contracted the disease in the town had not been vaccinated with this serum, while 100 or 200 who *had* been vaccinated escaped, although they were equally susceptible and equally exposed.

SUMMARY

The following are the significant facts:

Of the 17 cases occurring at the College, all received the Noguchi Serum.

Of these, 4 were already in their 4th to their 6th day. All died.

Of the other 13, all received the serum on their 1st or 2nd day. Only one died.

No cases occurred in the town among those who had been vaccinated. Of the 3 cases which did take place in the town, one received the serum not until about the 10th day and the case ended fatally. Another received it on the morning of the 4th day, and recovered. I do not know whether the fatal case in New Orleans received the serum or not; if so, it could not have been before the 5th day.

It is my firm opinion, based on experience gained in the 1905 epidemic, that several more cases would have ended fatally but for the serum treatment; and also more cases would have occurred in the town, had not the anti-yellow-fever vaccine of Noguchi been available. In the 1905 outbreak there was a mortality of over 20%, distributed evenly throughout the epidemic; in the 1921 epidemic, the mortality was practically confined to those cases which were treated

too late for the serum to be of any benefit. Among those cases that received the serum during the early stages of the disease, only one fatality occurred.

The town of Belize, being partly at and partly below sea level, from a sanitary point of view is a hard problem. Most of the low-lying areas are in communication with the sea, and contain either salt or brackish water. This condition, while favorable to certain species of the mosquito pest, is not much appreciated by either the Stegomyia or the Anopheles variety. Breeding places for these species, however, are many: (1) the rain-water containers, ranging from vats to barrels and kerosene tins, on which the inhabitants solely depend for their water supply; (2) the numerous depressions holding fresh water during the wet season; and the empty tins and similar rubbish which accumulate in many of the yards.

Although there exist thoroughly efficient and model laws dealing with mosquito-destruction, it is very difficult and irksome to be obliged to continually enforce them, and the town was lulled into a sense of security as a result of its fifteen years of immunity from the plague.

Upon the discovery of the outbreak, an appeal was made to the Rockefeller Foundation, and the reply was both prompt and effective. In a very short time Dr. E. I. Vaughan and Mr. B. R. Dyer, of the Foundation, arrived with an almost unlimited purse, and with an equally unlimited supply of that energy and tact which is so necessary for the successful and smooth working of all public health measures.

An executive commission was appointed, an adequate staff enrolled, and an energetic campaign established for the systematic inspection of the town, oiling and screening of water receptacles, and the thorough cleaning of yards. Within a few months these measures were accomplished to such an extent that the mosquito index fell from 50% to within the 5% safety line established by the Foundation. It has remained at that point ever since. I thoroughly agree with Dr. Agramonte that the anti-mosquito work should be continued. I should consider the Noguchi treatment as being of value only in the midst of an actual outbreak.

The Foundation worked with us for a year and accomplished a maximum of work and education with a minimum of friction.

The services of a thoroughly qualified sanitary inspector were then obtained, and both the staff and the system are being efficiently maintained. This is true not only in Belize, but in all the principal towns of the Colony, especially those on the seaboard.

It is interesting to note that this sanitary inspector — Mr. J. H. Peach — is gradually persuading the householders to substitute for the costly wire-screening method a system of "fishing" the tanks, with a species of small fish known locally as "Billums." They live well in the tanks, and a couple of them are able to keep any ordinary tank free from mosquitoes. All public and many private water-containers are now stocked with the fish, and there is still so much demand that the supply is not adequate.

Belize is much in need of extensive reclamation work and a pipe water-supply. The latter would be very costly, as no supply by gravity is available.

The town is not wealthy, and, up to the present time, no rich uncle or fairy godmother has come along; but it is still in hopes that the necessary improvements will be accomplished, even if it has to apply to the "well-known uncle" for a loan.

Belize is not unhealthy. It has had only two small outbreaks of yellow fever during the last 30 years. Curiously enough, they occurred at 15-year intervals, and each was stamped out in less than six weeks.

Strong sea breezes blow for about 8 or 9 months in the year, the temperature very rarely reaching 90 degrees. Zymotic diseases, except those of childhood, are practically unknown, and the class commonly known as tropical diseases is comparatively rare. The anti-mosquito campaign is already showing results in the form of reduced hospital admissions for malaria. Europeans live there for 30 to 50 years in the best of health, and, like myself, are apparently taking only one serious risk — that of dying of Senectus.

SOME OBSERVATIONS UPON YELLOW FEVER PROPHYLAXIS

ARISTIDES AGRAMONTE, M. D.

The last word has not been said upon all the means that might be advantageously employed to prevent the development of yellow-fever epidemics, or to stamp them out, once that they have developed, nor do I pretend to say it now or ever, nor will any one perhaps have the opportunity, until the problem of its etiology be clearly and definitely elucidated.

Unfortunately, from the time of the admirable conception of Finlay's which placed the guilt of transmitter upon the Stegomyia mosquito (then so called) until the present day, much of the research has been taken up by the thankless task of setting aside erroneous methods and deductions. To mention only the names of Freire, Carmona y Valle, Gibier, Sanarelli and Seidelin, brings before our mental vision a fantastic array of hopes deferred after glorious promises, with failure and disappointment at the end. In the case of Finlay himself, twenty years elapsed before his theory was accepted, simply because all his efforts to prove it were in vain: The lack of technical resources in some of the details of his experiments and his inability, therefore, to produce an unquestionable case of yellow fever by the methods he employed, caused his theory, which was nearly perfect, to be received with disdain or unbelief by nearly all his contemporaries.

It was left for the United States Army Board, appointed by Gen. George M. Sternberg, of which Maj. Walter Reed was chairman, to clear the chaff from the grain, to change Finlay's wonderful theory into a doctrine, and so, immediately after, as at the waving of a magic wand, the disease was stamped out in Cuba, then in Vera Cruz, New Orleans, Laredo, Rio de Janeiro, etc., becoming thenceforth relegated to a few of the South American and West African ports.

The findings of the Army Board were the basis upon which all subsequent campaigns against yellow fever rested: The

period of infectivity in man was so determined that nothing different has been demonstrated, though much has been said to cast a doubt upon it, in the natural tendency to make new theories and new findings fit each other; and so the methods of treatment of epidemics have been clearly outlined, and set down, and carried out since then with the results that you are all familiar with.

All this notwithstanding, yellow fever retains a hold upon certain portions of this Continent. It appears to die out here and there, only to reappear again, making the greatest demands upon the imagination of those who are expected to extinguish it forever, to explain the why and wherefor of such relapses. This has been the case in certain parts of Brazil, in Mexico, on the West coast of Africa, and today in San Salvador.

In dealing with the prevention of yellow fever in any community or state, we have to depend upon two great factors: immunity of the individual — either the so-called natural or the acquired immunity — and the adequate prophylactic measures that may be implanted, given the conditions of the country, the general environment, and the habits and character of the people.

Of course, the stamping out of an epidemic and the preservation of a community from its invasion, are two entirely different things and each must be met in a different way. The former demands, on the part of the sanitarians, greater knowledge of the epidemiology of the disease, the putting forth of greater efforts, greater expenditure of public and private funds, while the latter simply requires alertness in obtaining information regarding dangerous neighbors, a low level of mosquito incidence, and unflagging energy in maintaining the proper quarantine restrictions. There are many cities, in both North and South America today, that depend for the exclusion of yellow fever mainly upon their vigilance and their port conditions.

In looking over the literature upon the subject, it strikes me as rather remarkable, how sanitary officers usually pay so little attention to the demonstrated rôle that children play in maintaining the endemic conditions in various localities. I believe the existence of such latent source, originally pointed out by our Guitéras, to be the cause of epi-

demics at long intervals, without the introduction of new cases. History shows that months, and even years, have elapsed between the last well-known and authenticated case of yellow fever in many places, and the reappearance of the disease in the shape of a new epidemic; it would be difficult if not impossible to explain such phenomena, except by admitting the probability of the persistence of the infection, in a mild or atypical form, amongst the children. A careful investigation would often reveal, I am sure, the occurrence of cases of so-called gastric fever, bilious fever, or what not, among the younger population; this will usually coexist with some degree of neglect of the sanitary ordinances regarding mosquitoes and their breeding places.

Let us consider for a moment the fundamental truths with reference to the etiology of yellow fever, based upon which all the prophylactic measures must be implanted. These facts run parallel with such as we know to be etiologic in the malarial fevers.

In the first place, the parasite is one that requires a mosquito as intermediate host before a secondary case may be derived from any given source; secondly, this organism is present in the peripheral blood only during a clearly defined period of the disease (the first 3 days, possibly 4 days); thirdly, a definite period must elapse before the mosquito is capable of transmitting the parasites in condition to reproduce the disease in man (about 12 days); and fourthly, there is a period of incubation, which all sanitary authorities agree, today, is not greater than 6 days before the appearance of the first symptoms.

Now, any prophylactic procedure that will tend to disregard any of the above points, or that may be neglectful of their careful consideration, is a dangerous one. So-called protective vaccination, as lately introduced in various parts of America, I place in this category, inasmuch as it conveys to those subjected to it, a sense of immunity which I doubt very much exists, and which has more than once failed to protect, although many reasons have been offered in explanation of its failures. If a sanitary campaign is fought upon the basis of the recognized and accepted facts above cited, the value of vaccination in yellow fever, when employed at the same time, cannot be demonstrated, unless the chances

of infection are not less for those vaccinated than for those not subjected to the operation; this is not the case when soldiers are used for the purpose, or any selected body of men, to the exclusion of the rest of the population. If a campaign is intended, leaving out of consideration the active destruction of mosquitoes—the infected, as well as the uninfected—the prevention of their development, and the isolation of cases during the early stages of the disease, then the community will suffer and pay a very high price for such negligence.

The protective vaccine at present used in yellow fever is one obtained from inoculations made upon animals with Professor Noguchi's leptospira. I must declare that this *Leptospira icteroides* presented as the causative germ of yellow fever, which readily and in most ways infects dogs and guinea pigs, fails to fit in with etiologic facts relating to the disease in man, as we know them to be. If Dr. Noguchi and his pupils, in a lesser number of cases, have demonstrated the leptospira in guinea-pigs inoculated with yellow-fever blood, others have failed repeatedly in the same quest. Of course, the failure here is usually attributed to a faulty technique, as in the case of Borges Vieira, working in the region of Nazareth, Bahia, and Lebredo, who followed very closely upon the savant's instructions, in Yucatan. This, I need hardly say, is not fair to what we might call the "negative" investigators.

I cannot pretend to say what *L. icteroides* really represents in the cases where it was found by its discoverer, nor could I justly cast any doubt upon the diagnosis of any of the cases, difficult as I know it to be in a great many instances, but the serologic differences between *L. icteroides* and *L. icterohemorrhagiae* are not pronounced; in fact, they are no greater than those we find between other organisms that form part of a single group, showing them simply to represent different strains; yet, yellow fever and Weil's disease are clinically and pathologically entirely unlike.

If the leptospira were really the causative germ, it would have the privilege of being the only spirochete transmitted by mosquitoes: In the cases of the other insect-borne diseases of like source (spirochetoses) the insects act as simple vectors or carriers of the germ, while we have reason to

believe that in yellow fever the parasite must undergo some kind of evolution in the mosquito's tissues, just as the malarial parasites do in the Anophelinae.

I have not heard of any one's attempting to demonstrate an insectile evolution of *L. icteroides* in *Aëdes aegypti*. An enriching process has been suggested, but that is only a hypothesis to explain the occasional success in the midst of many negative experiments. We know that no changes take place, and that the mosquito soon expels the leptospira, just as it took it from the capillaries of the guinea-pig.

The experiments of Professor Noguchi and his disciples, by which they isolated the organism, *Leptospira icteroides*, when injecting yellow-fever blood to guinea-pigs, are most interesting from a bacteriologic standpoint, but to my mind, they have served to lead to most erroneous conclusions from the facts apparently at hand

The specificity of *L. icteroides* in yellow fever, I believe, is as far from being proved as it was at the commencement of the researches in Guayaquil, where Dr. Noguchi saw it first. Guitéras, Lebredo, Recio, are with me in this opinion. The slight support obtained from other workers seems to show this leptospira as a possible symbiotic organism in cases of yellow fever, possibly the one inducing the hemorrhagic phase of the disease. The symptoms, the pathologic and histologic lesions, and the hematologic conditions which *L. icteroides* causes in animals, are very closely related, if not identical, with those caused by *L. icterohemorrhagiae*, the etiologic factor in Weil's disease, as demonstrated by Hoffman in Havana.

I am not going to make a further criticism of Professor Noguchi's leptospira; it would require very much space and time, such as I am not warranted in taking at this opportunity, but I must call attention to the danger involved in accepting as final some of the points being brought out as pertaining to *L. icteroides* if we consider it as the parasite of yellow fever. For, if we do, we shall soon have to modify many of our views regarding the epidemiology of the disease, in a way that will affect our present quarantine regulations and the method of their application, not the least important of which is the period of incubation, now estimated as 6 days, and the minimum 18-day limit, with reference to the possi-

bility of secondary cases, as so ingeniously figured out by H. R. Carter, in the Orwood and Taylor epidemic of 1898.

A prophylactic vaccine and a curative serum derived from *L. icteroides* I believe to be of very questionable value. On the other hand, it may cause a false sense of security in the minds of those who are unable to study the subject sufficiently. When a mosquito infected from an inoculated animal is, 12 days afterward, made to bite a non-immune individual causing thereby an undisputed case of yellow fever, all other sources of infection having been excluded, then will be time to accept the specific character that is now attributed to Professor Noguchi's germ. But so long as experiments and tests are restricted to the lower animals, trying to determine therefrom the value of the so-called vaccine and sera in yellow-fever prophylaxis, *L. icteroides* can have but a laboratory interest. It cannot be argued that this experimentation in the human being is accompanied by great risk to life; the United States Army Board had no fatalities in a series of more than 18 cases which served to demonstrate the theory of mosquito transmission, and I believe that a wise selection of the subjects, and their subsequent care, should they become infected, would insure no death rate.

Another objection to the latest procedure is that if much reliance is placed upon vaccination, as we see it occur with reference to other infections, other methods of protecting the community, if not neglected entirely, will be performed half-heartedly, to the sorrow of all concerned.

It might be better, far better, to pay less heed to statistics of vaccine protection where such a factor as the eventual infection in a contaminated community cannot be controlled, and subject the matter to a more decided and reliable test. In 1901 we very quickly proved, in Havana, the real value of a so-called protective serum, and it took no more than a week to do it. I wish that we could submit the present vaccine to such a trial as was employed with the Caldas-Bellinzaghi serum. The harm that might be done to a single individual or to a few, would be much less than would result to the whole population of a town or city if it pins its faith upon an uncertain or useless measure.

One cannot but admire the remarkable work being carried

out by the Rockefeller International Health Board, its far-reaching and beneficent results in the control of infectious diseases, where the local authorities alone are unable to contribute the necessary means in men or money. The campaign against yellow fever, however, will suffer from the effects of this vaccination if too much confidence comes to be placed upon it. We have seen, repeatedly, that wherever the well-known methods are relaxed, even for a short time, the disease has reappeared or, as I believe, cases have simply increased in number, the infection extending among the foreign population and thus becoming more evident than when it remained limited to the natives alone.

We have in mind the case of Salvador and of Tampico, from which our sanitary authorities have not yet been able to remove the restrictions of quarantine. We have seen yellow fever apparently die out, only to reappear again in such spots as Yucatan, Northern Brazil, recently, and at long intervals along the West Coast of Africa, as it happened last year, and again at the present time. We have not yet learned, in an unmistakable manner, how the fever came into any of those places after they had enjoyed so many months or years of actual indemnity, nor how, for that matter, it got into some of the other epidemic foci that are sometimes accused of having been the source of the infection. I think that if more attention were paid, as in former times, to tracing the origin of the local epidemics, prophylactic measures would more readily and effectively strike at the root of the evil. Such methods were followed in Havana, Santiago, Laredo, New Orleans, Belize, etc., and the positive and lasting results you are all well acquainted with.

After the disease has been stamped out in a given locality, one must depend, for its permanent exclusion, upon quarantine. This cannot be relaxed unless the countries or regions of the country from which the infection might be reintroduced are kept upon strict surveillance, or their authorities have given proof of honest notification of cases, so that confidence may be placed upon their reports. This measure of quarantine, based upon a 6-day period of incubation, has already been demonstrated as absolutely reliable; the Panama Canal Zone, New Orleans, and other southern ports of the United States, and all the Cuban ports are good ex-

amples of the value of quarantine against yellow-fever invasion. In the latter (the Cuban ports) for instance, other preventive measures have practically become obsolete and although, since the last Cuban case, about 20 years ago, several have come to our shores from Mexico and elsewhere, they were readily taken care of and no secondary cases developed.

I would warn sanitarians to be wary of recent attempts to estimate the period of incubation as of longer duration, based upon results obtained by experiments upon animals. It is rather late, after the painstaking deductive work of Carter and the thorough investigations upon man by the Army Board, which fixed upon a maximum of 6 days as the incubation period in yellow fever. This was a stumbling block to all previous investigators, and the most sagacious of them were usually mistaken, until 1901, when it was discovered that a case of yellow fever could be developed at will and observed from the very moment of its inoculation, as was repeatedly done by us, applying infected mosquitoes or injecting blood subcutaneously, and in 2 cases by injecting filtered serum.

In conclusion, I beg to recommend that we do not swerve from the path heretofore followed by the pioneers in yellow-fever prophylaxis, unless it be to introduce such measures as may be necessary to meet peculiar conditions of the country, and that only, if they in no way weaken the fundamental structure of anti-mosquito campaigns.

DISCUSSION

Sir James Kingston Fowler (*Opening the Discussion*). — As the attention of the Conference at the present moment is centered on the results of the Noguchi Treatment, and not upon the history of the epidemic in Belize in 1921, I do not wish to distract attention from that very important point, one in which we are all greatly interested. In 1921, it fell to my lot, as a member of the Advisory Committee of the Colonial Office, to investigate the outbreak at Belize, but the conclusions at which I arrived were, I am afraid, somewhat different from those which have been placed before you. If I should go into them, I should do what I said I do not wish to. Therefore, I shall only state those conclusions briefly, as follows:

That yellow fever was endemic in Belize at the time the students returned to the College; that the students did not bring the disease

to the College; and that the first three cases were Indian servants, who alone went into the town — and naturally they were the first to be infected. The same thing exactly has happened in epidemics in West Africa, where the "Syrians" correspond to the Indian servants. There they are the persons most nearly European in blood who mix with the population, and in consequence the epidemics most often start with the "Syrians." In Belize, as I have said, it started among Indian servants in the College. I know nothing about the effects of the Noguchi prophylaxis and treatment, and, as I do want to hear about it, I will not occupy your time any longer in regard to the introduction of yellow fever into Belize in 1921.

Dr. Hideyo Noguchi. — The main concern expressed by Dr. Agramonte seems to be that the introduction of vaccine and serum into the campaign against yellow fever will lead to disregard of the time-honored, routine sanitary measures, so successfully carried out during the past twenty-five years, and based on the memorable work of Reed, Carroll, Agramonte, and Lazear, and of Gorgas, Carter, and their associates. I may state at once that retrogression of this kind is most improbable. When specific prophylaxis and serum treatment for yellow fever were suggested, special emphasis was placed upon the fact that they were supplementary means of fighting the disease and would not supplant the method of elimination by the anti-Stegomyia campaign, which is the ultimate measure to be employed.

We all know that effective anti-mosquito campaigns can make the Tropics safe for newcomers, and the time may be not far remote when yellow fever will completely disappear from all tropical countries, as it has already disappeared from Havana, Panama, Guayaquil, Rio de Janeiro, and other cities which were formerly endemic centers. There still exist, however, certain regions where it is difficult to maintain sanitary measures satisfactorily, and where yellow fever occasionally prevails. The vaccine and serum are intended, the one to give certain non-immune persons temporary protection until the Stegomyia index can be brought sufficiently low, the other to give the patient the possible benefit of a curative serum without neglect of symptomatic care. In fact, all non-immune sanitary inspectors working in the infected areas under the auspices of the International Health Board, in coöperation with the public-health authorities of the various South and Central American countries, are now being vaccinated.

With regard to Dr. Agramonte's objections to *Leptospira icteroides* as the cause of yellow fever, time will not permit my entering into categorical discussion here. One point, however, that I wish to emphasize is the importance of proper facilities and tech-

nical training in this rather specialized branch of experimental research, a point which I believe cannot be over-emphasized.

Dr. Agramonte bases most of his objections to *L. icteroides* on the experimental work of Lebredo and Hoffmann in Havana. Yet if one carefully analyzes the experimental protocols presented by these workers, one will find that more than 60% of the guinea pigs inoculated by Lebredo began to show fever within 6 to 30 hours, and many of those inoculated by Hoffmann had a *leucocytosis* of 20,000 to 40,000 within the first 24 to 48 hours. In our experiments these phenomena occur only in instances in which secondary invasion by another organism is present. The incubation period in uncomplicated *icteroides* infection varies from 3 to 6 days, and is seldom as short as 40 hours. The paratyphoid bacillus, a normal inhabitant of the guinea-pig intestine, very often complicates the *icteroides* infection and produces early fever and enlargement of the spleen and lymph nodes. In tropical laboratories (Mexico, Peru, Brazil) this complication has been one of the most troublesome encountered in our experiments. The outstanding and constant features of experimental *icteroides* infection in guinea pigs, puppies, and certain monkeys, are, in our experience, gastro-intestinal haemorrhages and pronounced fatty degeneration of liver and kidney, jaundice and albuminuria, and relatively slow pulse.

Yellow fever and infectious jaundice are both caused by a filterable microörganism, are non-contagious, and are characterized by jaundice, haemorrhages, acute hepatitis and nephritis, and so-called relative brachycardia. In both diseases an attack confers lasting immunity. The clinical symptoms, according to my personal observations, are very similar. *L. icterohaemorrhagiae* was isolated from infectious jaundice by Inada and Ido in 1914, and *L. icteroides* was isolated from yellow fever by myself, in Guayaquil, in 1918, and in subsequent years by several others during different epidemics. Morphologically, *L. icteroides* is slightly thinner and shorter than *L. icterohaemorrhagiae* or *L. hebdomadis* (the cause of "seven-day fever"). Serologically, *L. icteroides* gives a positive Pfeiffer reaction with the serum of yellow-fever convalescents, while *L. icterohaemorrhagiae* does not. It is significant that most spirochaetal infections are insect-borne and that certain spirochaetes are filterable and pass through a developmental cycle in blood-sucking insects.

Animal experiments have yielded no evidence which conflicts with the observations on human yellow fever such as form the basis of sanitary and quarantine regulations.

In conclusion, I wish to repeat that the vaccine and serum should

not interfere with established sanitary regulations against yellow fever or with the usual symptomatic treatment of the disease.

Dr. Henry Rose Carter.—The question concerns, not yellow fever, but the efficacy shown by the vaccine of the culture of *Leptospira icteroides*, and by the serum made from that same culture. It is possibly unfortunate that you called upon me, because it would be hard to find one who has less personal, first-hand knowledge of this thing than I. I have, however, some knowledge of the statements and writings of other people, on the subject.

When Dr. Noguchi returned from Guayaquil, I went to see him as soon as I knew of his claim. He showed me everything he had to show. There was nothing he kept back from me. To me the question was whether he had derived his parasite from cases of yellow fever, or from cases of *L. ictero hemorrhagica — Weil's disease.* I had had much to do with yellow fever, and had been what Americans call "the goat" in making diagnoses in many first cases, and knew how easy it was to mistake one for the other.

At that time I had seen but five cases of *Weil's disease;* I said, then, that if I saw these occurring in a yellow-fever zone in cities of the southern United States I should suspect them of being yellow fever; and that if they occurred during an epidemic of yellow fever, I should so consider them, almost without examination. It was not easy to distinguish between the two.

In Guayaquil, Dr. Noguchi reported that over 60% of the rats examined showed ictero-hemorrhagica. The association of people with rats in Guayaquil must have been very close, because bubonic plague among the population was common there at that time. It was reasonable, then, that from time to time in that city cases of *L. ictero-hemorrhagica* should occur among human beings. None had ever been reported there, although some have been recorded since that time. If such had occurred there previously, and it was probable that they had, they must have been considered yellow fever. And, frankly, if I had seen them, I should have accepted them as yellow fever cases unless there had seemed some reason for making a critical examination, which of course would have disproved such an hypothesis.

The first thing I noted when Dr. Noguchi showed me the autopsies of guinea-pigs, rats, etc., killed, some by *Leptospira icteroides*, some by *Leptospira ictero-hemorrhagica*, was that the *results* of infection differed in degree, but not in kind. The infection from *Leptospira icteroides* was more jaundiced, and less bloody, than that from the Japanese strain of ictero-hemorrhagica, but both were bloody and both yellow; and when a mere clinician in a laboratory is attempting to distinguish by degree, he is on difficult ground. Similarly, while the cultures were not exactly alike, they differed

in degree only. I could not distinguish them by morphology except in degree.

I suggested to Dr. Noguchi, then, that there was a chance that Pareja — who is a good diagnostician — had given him, amongst the cultures of yellow fever, some of *L. ictero-hemorrhagica* (an error that any man might make, in atypical cases) and that he (Noguchi) might have been working, not with yellow fever, but with Weil's disease. Further, I suggested that the thing for him to do, was to compare the immunological characteristics of ictero-hemorrhagica with those of his *Leptospira icteroides*, to see how they compared, and that he should use for this purpose, not the Japanese strain but the Guayaquil strain. I knew that there was sometimes a decided difference, in immunological reactions, between the different strains. Dr. Noguchi acted upon my suggestions.

As you well know, a mere clinician and sanitarian is little more fit to judge a distinctively bacteriological problem, than a layman is to pass judgment upon a medical problem. Taking at their face value Dr. Noguchi's findings of the serological reactions of his cultures with yellow fever cases and the ictero-hemorrhagica cases, when I went to Peru in 1920 I felt that I should not hesitate to accept this organism as the cause of yellow fever, and accept it without reserve. Basing my judgment on his findings, I don't see how any one can escape coming to the same conclusion.

I carried down to Peru a certain amount of serum, which I religiously kept on ice, and I carried vaccine. I had no occasion to use the serum, during a stay of about twenty-two months. I saw but three cases where there would have been any chance to use it. At that time, before you could get a Peruvian physician to allow you to use serum on a patient you had to make two statements: (1) that the man would certainly die if he should not receive the serum; and (2) that he would certainly recover if he received it. It is difficult to make those two statements in regard to anything.

When I first reached Peru, at Payta I saw an American engineer, Carlson, by name, with an abscess on his shoulder, where he had received the vaccine from Dr. Kligler only a few days before. I was extremely desirous of giving him serum, for he had been sick only about six hours; but his physician, a Peruvian, asked me whether he would certainly not recover without it. I couldn't definitely say that, — so Carlson got well without the serum. Two or three people had already died.

During my stay in Peru I found not a single case in which the physician would allow the serum to be used if there was the slightest chance of judging of its effect. Restrictions were nearly as bad

in regard to the vaccine. At that time the vaccine used contained agar, and, I think, in the hands of Drs. Kligler and Valcarcel caused, roughly, 100% of necrosis. Unless a man had been directly exposed to yellow fever, he would not let you give him vaccine. Carlson's case too, a severe one, occurring after vaccination, although too soon after for protection to be expected, did not encourage vaccine's being used.

I have seen a good deal of vaccine given, and have myself given it; but never have I seen it given when one could judge of its value, because it was given without proper controls. In looking over the literature I note that Lyster, Noguchi, and some others are very much in favor of it. I examined a good many reports from various places on the use of vaccine, but I can't say that any of them satisfied me. These reports show that vaccine would be given to, say, 300 people, none of whom developed yellow fever, but that generally there was no control.

The only place I know of where there was control, was Tuxpan, in Mexico. It is so long ago since I studied those reports that I do not remember the exact figures. I would say, roughly, that 4,000 persons were vaccinated, and that 2,000 were not. A much smaller proportion of the vaccinated — say, one-sixth, or possibly one-tenth — had yellow fever, than of the unvaccinated. Yet these data are not entirely satisfactory, because we do not know that the two groups were equally exposed.

A city is not uniformly infected. There is enormous variation. In 1897, you could go to one part of New Orleans and find 1% of the population infected with yellow fever, and go to another part and find 20% infected. I wrote to Dr. Noguchi about this, and in a personal letter he stated that those who were vaccinated had been more exposed than the others. In the light of this authoritative statement, the Tuxpan statistics were eminently satisfactory. No such statement was in the report, however. It is all very well to vaccinate a man, and then have him develop no yellow fever. But unless for vaccination you can get two groups of men, groups of considerable size, the one vaccinated, the other unvaccinated, and both groups equally exposed to yellow fever, you cannot judge of the efficacy of vaccination.

In the first attempt at vaccination — in the case of the battalion of the Vincedores, about 500 men from the Andean plateau — some 300 were vaccinated, and then the others came down and were vaccinated also but with a smaller dose. Among the first group there was extremely little yellow fever; among the second slightly more. But it cannot be said that there was any real control. If Dr. Noguchi had broken his flask of vaccine after the first group came down, he would have had control. I have then

no personal knowledge that either vaccine or serum has been tried under conditions which would allow one to judge of its efficacy.

A reading of the reports of the first vaccinations made in Guayaquil, and of those made in Tuxpan, inclines me to think that the vaccine is of very considerable value; and the statements made today of the results at Belize, though not sufficient to *establish* the value of vaccination, do lead to belief in its efficacy. From first-hand knowledge, I don't know anything about it. This is almost a layman's opinion.

I accepted this *Leptospira icteroides* as the casuative organism of yellow fever, not because of my own findings, but simply from the statements of Dr. Noguchi. If his statements are true, and I have every reason to believe they are, to me the conditions for belief in his results are satisfactory. I have vaccinated a number of people going into the Tropics — and I shouldn't think of allowing my daughter to go into the Tropics without being vaccinated — but that is only evidence of my belief in the value of vaccination, and not evidence of such value. The instances of Tuxpan and the other places that have been mentioned are evidence *indicating* the value of Dr. Noguchi's serum and vaccine, but do not *prove* their value.

Dr. Hideyo Noguchi. — I am greatly interested in Colonel Cran's report, and appreciate his having carried out a thorough and careful personal study of the effect of the yellow-fever vaccine and serum. His results conform with those of a number of other workers who have used the vaccine and serum during epidemics elsewhere. For example, a report issued by the Department of Health, of Mexico, gives the following statistics of serum treatment for 1920:

Month	Total number of cases	Cases Treated with Serum			Untreated Cases		
		Total	Recovered	Died	Total	Recovered	Died
Sept.	36	0			36	17	19
Oct.	40	13	11	2*	27	11	16
Nov.	34	2	1	1*	16	20	17
Dec.	13	4	4	0	9	4	5
	123	19	16	3	106	49	57

*Treated on the 5th day of disease or later.

Dr. Henry Hanson, who successfully fought the 1920-1921 epidemics in northern Peru, where 10,000 to 15,000 persons are estimated to have had yellow fever, made the following statements in an address delivered in Panama on November 26, 1921:

We had serum, but as there exists a certain prejudice against vaccine or serum, we were unable to make extensive observa-

tions on this point. However, of 8 soldiers to whom we applied the serum treatment, only 2 died, which seems to be a good indication of the efficacy of serum in the treatment of yellow fever. In untreated groups of the same sort of people who did not get serum, we had up to 100% deaths.

In regard to vaccination, Dr. Hanson said:

> We vaccinated about 1,000 persons. In Lambayeque we vaccinated about 200 soldiers, and had no case among them, in spite of the fact that they remained there before the fever had disappeared from the place. In Paijan, which was the worst place, we had no cases among 200 who had been vaccinated, and these people were vaccinated very early in the game, when the fever was still very severe. We do not know if they were immunes or not. They gave us no assurance of having had the fever.

Dr. Joseph H. White and Dr. Theodore C. Lyster, who participated in the campaign during the epidemic of 1920, in Los Amates, Guatemala, both believed, as each stated to me separately, that the early abrupt cessation of the epidemic was due to the wholesale vaccination of the entire population, an opinion which carries much weight, in view of the extensive sanitary and epidemiological experience of these men with yellow fever.

Surgeon-General Orsonio, of the Mexican Army, had 600 soldiers vaccinated in 1921 before they were sent to Manzanillo, a town of 3,000 inhabitants, where yellow fever had just broken out. Although these soldiers remained in the town, and mingled with the people, during a period when many cases of yellow fever were occurring daily, none contracted the disease.

The vaccine was used in the fall of 1920, in Tuxpan, Mexico, where 86 cases of yellow fever had occurred during the period between August 20 and October 7. As an emergency measure, 2,000 persons, of the total population of about 6,000 were promptly vaccinated, most of them on October 7 and 11 and the rest between that date and November 5. Those vaccinated were professional men and soldiers, non-immunes, from the mountains and northern regions of the Republic; any persons who desired vaccination, however, received it. At least 1,000 individuals had already been immunized by the 21st of October, and the entire 2,000 by November 15 (allowing 10 days after the last injection for development of immunity). In the meantime, the epidemic claimed 39 victims among the unvaccinated group, between October 10 and 31; 18 between November 1 and November 15; and 28 between November 15 and December 19: — that is, a total of 85. The last case occurred on December 19. Among the vaccinated group, 2 persons

came down within 24 hours of the 1st injection, 2 within 5 days, and 2 within 6 days. Of 10 persons receiving a 2nd injection, 2 contracted the disease within 24 hours, 5 after 2 days, 1 after 3 days, and 2 after 4 days, from the time of the 2nd injection. These 16 cases do not indicate inefficacy of the vaccine, because in every instance the patient must either have been in the period of incubation (3 to 6 days) when vaccinated, or contracted the infection before vaccination had had time to produce sufficient immunity, about 10 days being required. Notwithstanding the fact that the epidemic lasted until December 19, and that 85 cases occurred among unvaccinated persons (101, if we count the 16 who contracted the disease before the development of immunity), and that these 2,000 vaccinated non-immunes mingled with the general population, not a single case of yellow fever developed among the vaccinated.

From data in our possession, there is definite indication that early use of the serum modifies the course of yellow fever favorably; at any rate there is no evidence that the administration of the serum has any unfavorable effect on the patient. The vaccine, likewise, appears to have been useful in reducing case incidence among those who received it sufficiently in advance of exposure (10 to 15 days). Statistics may not always be reliable, but having obtained data of similar results repeatedly in different epidemics, and by different observers, we are inclined to believe that the vaccination protects non-immunes for a certain length of time (about 5 to 6 months).

I have with me tabulations of some of the results of the use of vaccine and serum, which may be of interest:

Place and Population	Year	No. vaccinated, and physician in charge	No. cases yellow fever among vaccinated				No. cases yellow fever among unvaccinated during same period	Incidence	
			Before 10 days		After 10 days				
			1 injection	2 injections	1 injection	2 injections		Among vaccinated	Among unvaccinated
Ecuador		Noguchi and Pareja							
Quito	1918	149	–	–	3*	–			
Guayaquil	1918	176	1	–	2**	–	386	11 per 1,000	110 per 1,000
	1918–1919	102 Bd. of Health	–	–	–	–			
Honduras									
U.S.S. Chicago	1919	75	–	–	–	–			
Amapala	1919	425	–	–	–	–			
Salvador	1920	3,469 (1 inj.) 138 (2 inj.)	5	–	5	–	181		
Guatemala	1920	791 (1 inj.) 592 (2 inj.)	1	1	–	–			
Mexico									
Tuxpan 6,000	1920	2,000	–	17	–	–	85	0	21.3 per 1,000

*Received 1 c. c. only.

**Received 1 c. c. only of diluted vaccine.

STATISTICS OF VACCINATION—Continued.

Place and Population	Year	No. vaccinated, and physician in charge	No. cases yellow fever among vaccinated				No. cases yellow fever among unvaccinated during same period	Incidence	
			Before 10 days		After 10 days				
			1 injection	2 injections	1 injection	2 injections		Among vaccinated	Among unvaccinated
Mexico—Cont.									
Vera Cruz	1920	514 (2 inj.) 234 (1 inj.)	2	–	3	–	199		
Manzanillo 3,000	1921	600 (Orsonio)	–	–	–	–			
Honduras									
Belize	1921	146 (Gann)	–	7	–	–			
Peru									
Tambogrande 500	1920	47 (Noguchi and Kligler)	–	1	–	–	17	0	3.4%
Paijan	1921	200 (Hanson)	–	–	–	–	Not recorded	0	Not recorded
Lambayeque	1921	200 (Hanson)	–	–	–	–	Not recorded	0	Not recorded
Brazil (done in N.Y.)	1922–23	57 (D. P. Robinson Co.)	–	–	–	–			
Céará	1923	68 (Thomas)	–	3	–	1			

Place, and physician in charge	Year	Serum administered before 4th day			Serum administered after 4th day			Mortality among untreated cases during same period
		Total	Rec.	Died	Total	Rec.	Died	
Salvador (Lyster and Bailey)	1920	14	11	3*	28	15	13	51%
Guatemala (Lyster and Vaughn)	1920	3	3	0	1	0	1	68%
Honduras (Lyster and Pareja)	1919	1	1	0				
Mexico								
Mérida (Hernandez)	1920	4	4	0	4	0	4	80%
Vera Cruz (Bd. Health)	1920	16	16	0	3	0	3	(537 deaths during year)
(Bd. Health) Oct. (part of 1920 ser.)	1920	11	11	0	2	0	2	59.3% (16 of 27 cases)
Gutierrez Zamora (Le Blanc's rept.)	1920–21	17	17	0	1	0	1	100%

*Received 20 c. c. only; "too small an amount to have any material effect" (Dr. Bailey).

STATISTICS OF SERUM TREATMENT—Continued.

Place, and physician in charge	Year	Serum administered before 4th day			Serum administered after 4th day			Mortality among untreated cases during same period
		Total	Rec.	Died	Total	Rec.	Died	
Mexico—*Continued* Tuxpan (Lynn)	1920	36	27	9	38	21	17	68.8%
Peru (Noguchi and Kligler)	1920	4	3	1**				
(Hanson)	1921	8	6	2***				(up to 100%)
Brazil (Barreto)	1920	4	2	2	2	1	1	
(Borges Vieira)	1920				1	0	1	
(Cavalcanti)	1920	12	11	1	5	4	1	
Céará (Thomas)	1923	12	8	4				

** Patient subjected to forced journey during first 2 days of illness; disease extremely severe; patient exhausted, with severe nephritis, when admitted to the hospital.

***Day of disease on which serum was given not recorded.

If we include the cases reported by Colonel Cran, the total number of cases treated with serum is 244, of which 155 received treatment within the first 3 days, and 89 after the 4th day of illness. There were 132 recoveries and 23 deaths (13% mortality) among those treated early, as against 41 recoveries and 48 deaths (54% mortality) among cases treated after the 4th day. Among the cases occurring in the same localities during the same period of the epidemic, the mortality, so far as reliable records could be obtained, ranged from 51% to 100% as shown in the table.

Major Henry J. Nichols, M.D. — As the question of the etiology of yellow fever has been raised, I wish to go on record for the Army Medical School as accepting the *Leptospira icteroides* of Noguchi.

As soon as Dr. Noguchi completed his work, he kindly sent us a culture of this organism, and also cultures of the Weil's disease organism; and for the sake of the historical as well as the practical interest we did some work. First, we filtered the organism, and in the filtrate we could find some deformed Leptospira, instead of the regularly curved Leptospira. We found a few drawn-out organisms, which passed through the filter that was used — and, by the way, we had some of the original apparatus used by Walter Reed. This filtrate was infective for the guinea-pig, a fact that seemed to be one argument in favor of the organism. The next impressive thing, to our minds, was the fact that Dr. Noguchi could find this organism anywhere in the world where yellow fever was reported — in Guayaquil, in Peru, in Colombia, in Brazil, and in Mexico. Some of Dr. Noguchi's assistants could not find the organism; yet when Noguchi himself went there he found it. Some investigators said that this was not yellow fever. In that case it seems to me that there is no such thing as yellow fever.

Another fact which impressed us was that Stimson in 1905 recorded a *Spirochaeta interrogans* found in sections of a kidney from a case in the New Orleans epidemic. We now look upon the organism as the same one found by Noguchi. Then there are the immunological reactions, which appear to me quite convincing.

To make a long story short, we have accepted this organism, and I have given a number of injections of Noguchi Vaccine to persons going into yellow-fever zones, because I think the evidence is enough to warrant our using all the biological means we have at our disposal to combat this disease; and certainly one of these means is vaccine, and another is serum.

As Dr. Noguchi said to Dr. Agramonte, no one would think of substituting vaccine for sanitary measures, even if all were in entire agreement about the organism. There are, however, circumstances under which persons going into unsanitary areas would like to be

protected, and persons having yellow fever would, of course, like to have the serum if it is available.

To rely on sanitary measures alone, would not be doing justice to the situation. The problem is somewhat the same as that of our experience with typhoid fever. If the latter disease occurs, the sanitarians would have it handled entirely through the water supply, and the laboratory people would have it handled by vaccine, as they are doing in Havana today, but the man of the streets would feel that we should use all measures at our disposal, irrespective of the beliefs of any one group.

Dr. Juan Iturbe. — In 1918, in collaboration with my colleague, Dr. Gonzalez, I was able to isolate a culture of spirochaetae from the rats, in Caracas, exactly like the *Spirochaete ictero-hemorrhagica* discovered by the Japanese investigators. I was unable to determine whether this *spirochaete* belonged to the Japanese or the European strain. By contact with these organisms, I could establish infection. At the meeting of the Venezuelan Congress, in 1922, I presented a paper in collaboration with Dr. Gonzalez also, in which we showed that we had found a pseudo-*Spirochaete ictero-hemorrhagica* in the aqueduct water of Caracas. I employed Manteufel's method (1922). There was no need of putting a coating of paraffin over the liquid, because this organism is both aerobic and anaerobic.

With Noguchi's method, also, I obtained pure cultures. The inoculations in guinea-pigs gave negative indications at first, but after 8 or 9 days of incubation I obtained in animals a fever and subsequent clinical symptoms and anatomical findings of *Spirochaetosis ictero-hemorrhagica.* I am not sure where to classify these two organisms, and I should like to hear from some member of this Conference regarding that question.

Dr. William H. Park. — I have asked the Chairman whether he would allow me a few minutes to say a few words on how to control vaccination experiments. Of the question at issue I have absolutely no knowledge, but I have had a very large experience in testing the value of vaccines and serums, and I do know how difficult it is to form a correct judgment.

Many of us remember that during the World War a group of Mount Sinai Hospital bacteriologists thought they had identified the typhus bacillus. They made from it a vaccine for combating the disease. The vaccine was tried on groups of physicians and nurses in Serbia, and the results were thought to be very favorable. Gradually, however, the evidence for the bacillus became more and more doubtful, and finally the vaccine was discarded and the nature of the bacillus was discredited.

Yellow fever is now so rare that we should try to utilize every chance to obtain positive evidence as to the value of the vaccine and to do that we should, when possible, make control tests, and if that is impossible the full data should be given. If Dr. Noguchi and those others who have the opportunity to test out the vaccines, get and publish full details, that would help both him and us to weigh the evidence. It is important for those who are combating yellow fever, anywhere in the world, to form a conviction as soon as possible.

For instance, if I understand Dr. Noguchi correctly, his best example of vaccine control is in a town of 6,000 where 2,000 persons were vaccinated and 4,000 were not. These numbers, however, were correct only after all the 2,000 had been vaccinated. The complete vaccination required two months. During the first month, then, perhaps 1,000 were vaccinated and 5,000 were not vaccinated. If yellow fever occurred among those 1000 yet to be vaccinated, but not yet vaccinated, it was undoubtedly considered as occurring among the unvaccinated. If so, the numbers were not 2,000 and 4,000; but for the vaccinated, none at the beginning, up to 2,000 at the end; and for the unvaccinated, 6,000 at the beginning, gradually diminishing to 4,000. If we are uncertain as to the actual number of cases developing in a given time, and of the actual number of vaccinated and unvaccinated persons, it is difficult to put a value on the incomplete reports. We all know that cases are apt to occur in the first days of an outbreak, before effective measures have been taken to stop the development of other cases. Such details would give every possibility of utilizing the information to its full value.

Dr. W. E. Deeks. — When we obtain good results from the administration of specific sera, I believe, at times, they are misinterpreted. Frequently they are attributed to specific anti-bodies administered and supposed to be present in the sera. The good results which follow may be the result, in my opinion, of the administration of a foreign protein, as much as in the anti-bodies supposed to be contained in the sera. I have seen good results, in one hospital, follow the administration of a specific serum, and in another hospital equally good results follow in the same class of cases, by the administration of boiled milk. Surely in these cases we cannot attribute the good results to any specific bodies.

Dr. Aristides Agramonte (*Closing the Discussion of his Paper*). — I was very well aware that my modest contribution to this Conference was going to bring out adverse opinion, but inasmuch as I had been honored by an invitation to attend, I felt it was your due that I should give an absolutely honest opinion, my own, upon this matter, regardless of how it was to be received.

My original idea was to discuss this subject only from the sanitary standpoint. Prophylaxis, however, always brings us back to epidemiology, and as one of the methods of prophylaxis is by the Noguchi Vaccine and Serum, I had to come gradually to the subject of *Leptospira icteroides*, the supposed parasite, a subject which I should have preferred not to discuss today. I am not going to be drawn into a lengthy discussion of *Leptospira icteroides*, because I believe that experimental work should be neither repudiated nor accepted except after further experimental work; and in this direction I have done very little.

Dr. Noguchi knows that the only organism at our disposal was one strain, the "Merida" strain, that he very kindly let us have at Las Animas Hospital, in Havana. As I saw the work being carried out by Dr. Lebredo with this organism, I became more and more convinced, from my knowledge of the epidemiology of yellow fever that the "Merida" organism could not be the parasite of this disease. I want to say that I am absolutely convinced of the truth of Dr. Noguchi's assertions, and I wish to go on record now; but unfortunately I have become more and more convinced, by reading Dr. Noguchi's literature on the subject, that this cannot be the yellow-fever parasite. Such an expression of opinion, I can assure you, is not capricious, and it may require a certain amount of explanation.

There are two or three characteristics of this Leptospira which are not in accord with what we positively know about yellow fever. The first thing that impressed me when the original publication came from Dr. Noguchi's pen, was the very large quantity of blood which he has to inject into guinea-pigs in order to obtain the organism, in only a few of his inoculations. I am out of the research field now, but this seemed to me a very remarkable thing, when I knew that a tiny drop taken by the mosquito is quite sufficient, within 10 or 12 days, after due incubation, to bring about a case, with the precision of clockwork.

If a mosquito infected with the disease were to bite one of you men, a non-immune, I can assure you that within six days you would come down with yellow fever; and this certain infection upon a human being will be the result of a little drop of blood taken by the mosquito at the right time from the proper case. Now compare that with the massive blood inoculations of Dr. Noguchi, upon the little guinea-pigs, and the relative results obtained. We all know, those of us who have had any dealings with yellow fever, and all the authorities so recognize it, that it is *not* an oral infection.

We would have to go back to the old theories of "fomites" infection, if we were to believe that it is transmitted through the mouth, or by contact. Also, we know that non-immunes have

performed autopsies on yellow fever cadavers hundreds of times, that such persons have handled the patients, their black vomit, bloody sputa, etc., which would contain the Leptospira if this were the parasite, and yet that those non-immunes have never become infected through contact. And here we see that the Leptospira, by contact and by mouth, will infect guinea-pigs, dogs, and no doubt other animals.

I cannot get around these things, although I am open to conviction. Numerous facts have led me to doubt the specificity of *Leptospira icteroides*. To cite a first-hand instance: A female dog which was left at the Las Animas Hospital, in Havana, was suspected of having rabies. Within a few days she had a litter of nine puppies. Two of these puppies were infected by Dr. Lebredo with *Leptospira icteroides*. In due time, they developed Leptospirillosis and died. Autopsies were performed, and Leptospirae were found in their blood and tissues. Fifteen or twenty days after this, the mother dog was found to be very sick; she had been in contact with all nine puppies. We suspected she was going to develop rabies after undue incubation; but this was not the case, and she finally died.

Autopsy revealed the pathologic lesions of Leptospirillosis, and her tissues duly injected to guinea-pigs produced the disease. Immediately we suspected that this dog had been infected from her young, — but how? It could have been in only one way, by mouth, when she was in the act of licking her young and biting off their ticks and fleas, which she was often seen to do. In fact, Dr. Lebredo found hair of the puppies in her stomach. Neither the ticks, fleas nor mosquitoes could have been instrumental in causing her infection, for the other seven puppies remained normal the rest of the time. Here is a case of natural infection with the supposed parasite of yellow fever, by mouth, and in the light of my past experience, and that of every other worker in this field, I cannot believe that the parasite of this disease can be transmitted in that way.

It will take a lot of work on the part of Dr. Noguchi to convince me that such can be the case. I am willing to be convinced, and hope that I shall be in the near future, but an organism which in such expert hands has piled up such an amount of evidence against itself, I declare I cannot readily accept as the etiologic agent of yellow fever.

Lieut. Col. James Cran (Closing the Discussion of His Paper). — To many of us here whose work keeps them still under the shadow of a possible epidemic of yellow fever, it appeared to me that an account of the work done in the field, and the prophylactic measures employed, should be of some value, — at any rate until all

other measures are abandoned in favor of the prophylactic vaccine of Dr. Noguchi.

The theory that Sir James Fowler advanced, of yellow fever being endemic in Belize, was originally advanced by a local practitioner. This theory was, that the three Indians who had developed the disease, two aged men and a son of one of them, had been in the haibt of going down into the non-immune part of Belize, a small town of 10,000 inhabitants, and had there contracted the disease.

It was pointed out to this practitioner that he would have to account for the 14 original cases, as all of them had contracted the disease within 5 days of one another. One of them was this old Infirmarian, who had been sick for some time previously, and who very seldom came to the town, and we had the assurance of the Principal and others connected with the College that this man had not left that place for some weeks. Other cases were those of a Jesuit Father there, and of several students, so that the doctor had to account for how these got their infection at the same time as the Indians. He immediately dropped the hypothesis.

All medical practitioners were asked: How long do you think the disease has been endemic, if at all, in Belize? Has the death rate been increased? Have there been, in the last 15 years, any suspicious cases? They answered unanimously that they had not found any suspicious case there at all. So that I think we can take it that this theory was demolished, admittedly by its inventor.

In a small place like Belize where the white, or non-immune, part of the population is not differentiated in any way — that is, where the houses are all together — I think it would be impossible for a disease with a mortality such as yellow fever has had in the past, to lie dormant for any considerable time and not take its toll. Another argument that was used was: How do you account for the fact that those 14 cases all developed almost within a day, following the return of men from an infected area, no susp'cious case having occurred either before or after? The Rockefeller workers and the commission that sat on this epidemic of yellow fever, unanimously rejected the theory of town infection.

One point I forgot to bring out — that is, that there were 150 residents in this college who were exposed to a strong infection for 4 weeks. Of these, 17 got the infection all together, but not a single case contracted the disease who had had the vaccine for 10 days. I was very glad to hear Dr. Carter say that he believed in the Noguchi Vaccine, because in the 2 or 3 days in which we have got acquainted with Dr. Carter here, we have learned to know that his belief is well worth having.

I have not attempted to draw any conclusion, but merely to put the facts of the case before you. The 1921 epidemic in Belize, as compared to the 1905 epidemic which I also saw in Belize, reminded me of the difference in the treatment of diphtheria before and after the use of antitoxin.

PREFERENTIAL AND COMPULSORY BREEDING PLACES OF AEDES (STEGOMYIA) AEGYPTI AND THEIR LIMITS

HENRY R. CARTER, M.D.

Of course, the one absolute material requisite, (material as distinguished from conditional requisites such as temperature, etc.), for the breeding of mosquitoes of all kinds and in every place, is *water*. Fruitful oviposition of these insects, then, in nature, takes place only in relation to water: (1), present, at the time of oviposition for such as deposit their eggs only in water; or (2), water in the future for those which deposit their eggs in places free from water, but whose eggs will be covered by it at the proper time for them to hatch.

Given water then, *in esse* or *in posse*, it is common knowledge that some species, even some genera, of mosquitoes show decided choice as to the nature of the places they select for oviposition; and that where the desired places are available, they use them to the exclusion of other collections of water, or at least so much more frequently that other places are not a serious factor in the propagation of this mosquito. Nevertheless, we sometimes find that when breeding places of the preferred kind are *not* available, this mosquito will deposit eggs in other collections of water, although perhaps not in all kinds of such collections.

The class of breeding places first mentioned — *i.e.*, those utilized for oviposition when all kinds are available — we may call the *preferential breeding places*, or the *breeding places of election*, for the mosquito in question. The second class — *i.e.*, those in which eggs are deposited when, and only when, breeding places of election are not available — may properly be called *compulsory breeding places*. Naturally the places in which, in nature, eggs are not deposited even when these are the only collections of water available, are beyond the natural limits of even compulsory breeding places, and from the last two we may be able to determine the limits of breeding for this mosquito in nature.

Note, here, that when we speak of oviposition, or of breeding in any place or class of place, we mean oviposition, or breeding sufficient to be a serious factor in the propagation of this mosquito. When less than this, it is considered negative. This is, of course, rather the viewpoint of the sanitarian than that of the entomologist, yet for the sanitarian it is quite consistent. In Anopheles surveys, we grade breeding places as "of sanitary importance" and "of no sanitary importance," and disregard the latter. In yellow-fever campaigns, we count our work complete when the production of Stegomyia is so reduced that yellow fever cannot continue to be communicated by this insect, although a minimum production of Stegomyia may still be going on. So the occasional finding of a few larvae of a certain mosquito in places usually free from them, does not justify our classifying such places with those in which larvae are habitually found in considerable numbers. In sanitary matters (and I confess that I am inclined to look at mosquitoes from a sanitary standpoint) no one cares about *one* mosquito. It is only when zeros accumulate behind the *one*, and the mosquitoes can be counted in 100's, 1,000's or 10,000's, that they become important — to the sanitarian.

What we have said of the relation of oviposition to the different classes of possible breeding places, may be true of all kinds of mosquitoes. It is true of many kinds, but I am confining myself here and now to one — *Aëdes* (*Stegomyia*) *aegypti*, a known vector of yellow fever and dengue. I had purposed to take up the same question about some species of Anopheles, malarial vectors, but that would have made this discussion entirely too long.

It is a matter of common knowledge that for this mosquito the breeding places of election are collections of water in artificial (man-made) containers, or things that resemble them — wood, cement, etc. being preferred to metals as the material for such containers; and wood, especially a calabash, is preferred to cement. Yet, long ago, my attention was called, and rather dramatically, to the fact that these conditions of breeding, although usual, were not obligatory, and if lacking could be replaced by others. It was in Panama City, one Saturday, in the latter part of November or very early in December of 1905, and about the time that the last case of

yellow fever on the Isthmus for that year (Vaughn's case, at Colon) was reported. I had left the office and gone out to inspect the Stegomyia work in Panama City. With the man immediately in charge, Murphy by name, a very capable fellow, I visited a number of premises, houses, and patios. In all of these places, the *depositos* of water kept for domestic use were protected against entrance of mosquitoes. Cisterns: *tinajas: ollas:* all were empty or else covered, some with wire netting, some with cloth tied on, and some with well-fitting solid covers. Of a considerable number of premises that Murphy had inspected before I came he reported all as being negative for larvae and in none that I examined with him could I find larvae, or floating on the surface, pupa casts. The latter, in large collections of water, show up far more prominently than the larvae themselves, and in no house did I see Stegomyia in flight.

Yet in one place was I able to point out Stegomyia larvae, possibly ten or a dozen, in a rot-hole in a tree, and maybe twice as many, small ones, in the little collections of water in the axils of the leaves of some ornamental plants in the patio — a species of Colocasia. Guessing the cause for the oviposition in these places, and after a brief conversation, I directed Murphy to place — and assisted him in placing — a number of calabashes, ollas and other containers of water in shady and partly dark places around the house and patio, and I gave instructions that they should be emptied every Saturday, at the weekly inspection. The results were successful. Not only did I find this patio free from larvae the next three or four Saturdays when I inspected it, but I am persuaded that neither Murphy nor any of his men ever failed to make examination, or to provide for the elimination, from any other patio, of all such breeding places as those in which we had found those larvae.

It may be noted here that while we had already discovered that Stegomyia larvae were occasionally found in the small collections of water in the axils of the ornamental Colocasias, yet we had come to regard them as of minor sanitary importance, since only a small proportion of them developed into imagos. This indeed, seemed to be generally true of the compulsory breeding places of this mosquito. Her progeny seemed to have a much better chance of reaching

maturity in the breeding places of election, than in those places that she used only when the preferred localities were not to be had. The condition described may not be without exception, but the one exception that I have seen reported is not pertinent to our subject.

Since we had found that practically all of the preferential breeding places of this mosquito (the *depositos* of water) were inaccessible to it in the vicinity in which Murphy and I had found the larvae just mentioned, — and since we had not found larvae in rot-holes in trees or in the axils of Colocasia leaves elsewhere, it is fair to believe that the places in which larvae were discovered in this patio were breeding places of compulsion, used only because none more suitable were available. And this conclusion seemed to be, to some extent, confirmed by the experiment of making suitable breeding places accessible, whereupon the mosqitoes showed their preference for these.

What are the limits as to compulsory breeding places for this mosquito? On the Isthmus of Panama we did not find their larvae in marshes, or in seepage out-crops — so favorite a place for Anopheles — or in sluggish streams. We never found them in a street gutter, or in a roadside puddle, but that we were reasonably sure they had been washed in from some other place, as from an overflowing cistern or a sagging house-gutter. This was true, moreover, whether more suitable breeding places were available or not. In other words, such places were beyond the natural limits of breeding—complete breeding, from oviposition to imago — of this mosquito on the Isthmus of Panama.

Is this true everywhere or, as happens sometimes in the case of other mosquitoes, is there a regional variant relative to this part of its biology? Some years ago Dr. Francis, of my Service, as a result of his observations for some three years in and about Mobile, Ala., stated that "larvae of this mosquito have not been found in any collection of water the bottom of which was mud." Since that means "not in mud-puddles," it seems correct, and would be so accepted, I think, by all of you. As expressed, it doubtless was correct, anyway. The implication, however, that this was a general rule, and that the mud bottom of a collection of water was the factor which determined that

Stegomyia would not breed therein, is erroneous. During 1920 and 1921, in Payta, Sullana, Piura, Catacaos, and in practically every town in northern Peru that we examined, we found Stegomyia breeding, and breeding freely, in the great *botijas* or *tinajones*, used in that country to store water,—and this in spite of the fact that their bottoms were generally covered with mud from six to ten inches deep, or more. Very evidently, mud at the bottom of the water in no wise prevents their breeding in that water.

Granted that we have not found them carrying on the whole process of breeding in mud-puddles, what are the factors which prevent this? I think we can name one factor,—possibly the determining one. At Catacaos, a town of about 4,000 people, in northern Peru, where we had yellow fever in 1919 and 1920, there were many wells, say from 200 to 300. They were merely holes, dug from six to twelve feet deep, according to the depth of the ground water. We never found Stegomyia larvae in these wells, even when breeding was fairly well controlled in the artificial containers in the neighborhood. Plenty of larvae of other mosquitoes but none of Stegomyia. At Casa Grande, also in northern Peru, but farther south, in the house of every skilled employe there was a well, and we found Stegomyia larvae in exactly 100% of these wells! Why this difference? Could it be because the wells at Casa Grande were in occupied houses, while those at Catacaos were out in the open? It does not seem so, since the wells for general service at Casa Grande were out of doors, and all that we examined (some 8 or 10) showed Stegomyia larvae, although fewer than in the houses. There was another difference between the wells at the two places, besides some of them being indoors and some outdoors. Those at Casa Grande were lined with brick and cement, while those at Catacaos were unlined — simply dug in the clay. In Chiclayo, too, situated between the two places, there were a number of wells, some lined and some unlined. In none of the unlined wells that we examined did we find Stegomyia larvae; in none of those lined, whether with wood or with brick and cement, did we fail to find them.

Really this explanation had been anticipated by Dunn, who was working with Hanson. Any one who has seen the oviposition of this mosquito standing just at the edge of the

water, sometimes on the water and sometimes partly on the container itself, would naturally guess that the physical nature of the sides of the container *at the water's edge* might well be a factor in her choice of a place for oviposition. On the other hand, the nature of the bottom would be unknown to her, unless it affected the quality of the whole body of water.

After considerable more observation on this point in Peru, by Hanson and Dunn and their men, and after much inquiry oral and by letter, of men doing Stegomyia control work in other countries (Mexico, Yucatan, Central America, Panama and Colombia) I felt myself justified in presenting this formula, modeling it on that of Francis, as indicating the breeding places of this mosquito to be limited:

"*We have not found this mosquito in nature breeding completely, that is, from oviposition to imago, in any collection of water where, at the water's edge, there was nothing but mud.*"

This formula was thus given out, in a lecture, to the Laboratory Class of Officers of the United States Public Health Service, at Washington, D. C., in the spring of 1923; and, a little later, to a class at the School of Hygiene and Public Health of The Johns Hopkins University, at Baltimore, Md. As expressed, it was correct. Neither I, nor any one of whom I inquired, had ever seen Stegomyia breeding completely in the places excluded from this formula. Even the implication was logical and, I then thought, correct; yet I have recently learned that, taken as a universal formula, it is not correct.

Last September I received, through the International Health Board of the Rockefeller Foundation, copies of official reports — sent them from the British Colonial Office — on the yellow fever epidemics of 1922 and 1923 in British West Africa. Among these epidemics was one at Salt Pond on the Gold Coast, small but virulent, as African yellow fever has usually proved to be. In the report it was stated that the principal source of Stegomyia aegypti at this place, was the Lagoon and *the tracks in the mud around it* of the men and boys who go bathing there. The Stegomyia propagation was stated to be large, and uncontrollable except by means of a major engineering project. As illustrating the amount of this breeding, the report stated that in one mud

puddle about 10 inches square — characterized in it as "a typical Anopheles breeding place," — the larvae were so abundant that they formed a film on the surface of the water in the saucer in which they were dipped up. It was added that the larvae developed into imagos of Stegomyia aegypti and Culex fatigans.

The writer of the report, Dr. Lorena, and his immediate superior, Dr. Watt, both officials of the Sanitary Service of the Colony, ascribed this breeding "in such unusual places" to the complete elimination, from the town and its environment, of the usual breeding places.*

This, of course would mean that the breeding of Stegomyia aegypti in and about the lagoon was a compulsory breeding, there being no more suitable place available. Yet there are other reports, previous to the one quoted, implicitly charging that the Salt Pond Lagoon and its environment produced Stegomyia aegypti normally, *i.e.*, when there had been no interference with their normal breeding places. The report of Drs. Horn and Tytler, made in connection with the Yellow Fever Commission of 1920, of the International Health Board — the one on which Dr. Gorgas was serving when he died — implies this, although without definitely asserting it. It also implies that the same conditions exist at Secondee and other places on this coast. In some of the reports, too, (the last I saw were, I think, of 1913) of the British West Africa Yellow Fever Commission — of which Sir James Fowler was at one time the president — there were urgent recommendations for the abolition of this lagoon, and the remedying of the mosquito-breeding conditions around it, on account of their effect on the propagation of yellow fever at Salt Pond.

Be this as it may, neither LePrince nor I, nor any one of the many whom I have consulted, have ever seen in the Americas free Stegomyia breeding in mud-puddles, and this breeding at Salt Pond is reported as being not only free, but profuse. Nor have either LePrince or I ever seen this mosquito breeding in anything like the profusion implied in this report. Culex fatigans, yes; Stegomyia, never! It is a

* Why on earth, this being known, the "usual breeding places" in the town and its vicinity were not at once reëstablished one cannot imagine. Since it was known where they were, these could easily have been controlled. The breeding about the lagoon had been reported as "uncontrollable."

pity the reporter did not state the proportion of the two kinds of imagos developed from his mud-puddle.

Nevertheless I will not, on this account, reject this report as erroneous. I have seen too much of what, I suppose, we may call "regional variation" in the biology of mosquitoes, to refuse credence to a well-attested statement about them — as I consider this to be — simply because it is not in accordance with my own observations made in an entirely different region. And while I would greatly like to examine, for myself, the breeding of this mosquito in and about the Lagoon at Salt Pond, yet I feel that I should probably accept the statements of fact as given in the report quoted. Without denying it, I am, however, less inclined to acknowledge the breeding of the *Stegomyia aegypti* in and about the Lagoon at Salt Pond as its normal breeding there, *i.e.*, as taking place when water in artificial containers was available to them for oviposition. My reasons are, (1) The evidence for it, that I have seen, is less direct and less in detail; (2) It seems to me antecedently more improbable, and (3) In Lorena's report, these places (the Lagoon and the tracks around it) are characterized as "unusual breeding places" for this mosquito, used only because the usual ones in the neighborhood had been eliminated.

In any case, however, we must change the formula that I gave you, by limiting it to the Americas. And I am entirely willing to do this, because all that I know at first hand of Stegomyia breeding concerns its breeding in the Americas. Our formula should then read:

"*In the Americas* we have not found this mosquito, Aedes (Stegomyia) aegypti, breeding in nature comphtely, from oviposition to imago, in collections of water w ere at the water's edge there was nothing but mud."

This is not only correct, as expressed, but its implication that collections of water in the Americas under the conditions specified are not found breeding Stegomyia in nature is also, I am inclined to think, correct. For, since the receipt of the West African reports mentioned, I have been in communication, with reference to the breeding of Stegomyia aegypti in puddles, with a number of men whom I know and who are working, or have been working, in the Americas for the elimination of yellow fever. These men include White, Scannell,

Walcott, Carr and others in Brazil; Hanson and Dunn, an entomologist, in Colombia; Caldwell, Connor, Scannell, and Houle in Mexico, Yucatan, and British Guiana. No one has, so far, reported having found Stegomyia in nature breeding completely in mud-puddles, and a number report directly to the contrary. I think, then, that for the present at least, the implication of our modified formula, that complete breeding of Stegomyia in mud-puddles does not in nature occur in the Americas, may be accepted. This implication is supported by a considerable amount of evidence; negative evidence, indeed, but from the nature of the question no other kind of evidence is here possible. Is it enough — for negative evidence is convincing in proportion to its mass — to justify us in asserting that, in the Americas, mud-puddles are beyond the limits of natural Stegomyia breeding, even of natural compulsory breeding? I think so, but we should know definitely, when the work in Brazil is finished.

At any rate, there seems to be a variation in the limits of the compulsory breeding places of this mosquito in the Americas, from those at Salt Pond, and it may be at other places in West Africa. Possibly the biology of the African strain is less rigid than is that of ours; perhaps the African strain can adapt itself to conditions that the American strain is unable to meet. Well was it for us that this last was true! Had the Salada and all the puddles about Guayaquil produced Stegomyia, the elimination of yellow fever from that city would have been more difficult, even, than it proved. So, if the conditions of breeding as reported at Salt Pond are general in West Africa, the elimination of yellow fever therefrom will be decidedly more difficult than if the limits of the breeding of this mosquito, both normal and compulsory, were there the same as we have found them to be in the Americas.

Very obviously, then, the utilization, by Stegomyia aegypti, of breeding places other than those of election, and in addition to them, is of decided importance to sanitarians. It makes its control more difficult than if they used only the latter. If, as at Salt Pond, one must control its production not only from artificial containers in the town, but from mud-holes and ponds as well, the difficulty may be many-fold greater than if the first only were involved. And this difficulty might be *very* greatly increased if this adaptability of

the insect to breeding in what are now abnormal places, should prove to be a characteristic that can be cultivated and increased by practice, as has apparently happened with at least one characteristic of Anopheles maculipennis.

It would seem advisable, then, so to plan our methods of Stegomyia control as to limit, as much as possible, the use of compulsory breeding places by this mosquito. This plan will depend on the facilities available to the mosquito for oviposition. So long as the mosquito has easy access to enough breeding places of election, she will not seek to deposit eggs in any other. It may therefore be advisable to provide her with such breeding places of election.

Does the provision of suitable breeding places, of easy access to this mosquito of which we are trying to rid ourselves, seem a paradox? I have been asked (about Anopheles, however) whether I wished to encourage them to breed? Not exactly, but we don't care whether they breed or not, *provided there be no production.* As I answered my questioner, we are not trying to control the breeding, but the production, of mosquitoes. Eggs, larvae, and pupae are absolutely innocuous, and if breeding is stopped short of this final development into the imago, which alone is offensive, we are satisfied. Eggs and larvae, then, as many as you wish (pupae are too close to the final change to risk) *provided* there is no development of imagos.

Thus, control of mosquitoes (and this is a general rule applying to Anopheles, no less than to *Stegomyia aegypti*), by measures which allow of oviposition in their preferential breeding places, may be, and in certain places will be, the preferential method to adopt.

Now by the use of fish or of oiling (not a method of election) or by emptying water-containers at proper intervals of time, we can, in general, sufficiently control the production of Stegomyia, and yet allow this mosquito access to its preferential breeding places for oviposition. These methods involve no risk of driving the mosquitoes to unusual breeding places, the control of which may be difficult, or even impossible. Nay, even the removal of containers or covering them so as to prevent access of mosquitoes — methods very advisable for permanent work — can be used if other suitable and accessible breeding places be provided. The

production of imagos from these breeding places can be controlled: sometimes by means of fish; or by means of containers — as we know where we placed them — easily and absolutely, by emptying them at the weekly inspection.

It may be worth mentioning to you, that Fielding reports that a small amount of sugar added to the water increases its attraction to this mosquito, in its oviposition, although her progeny do not thrive on it. This is one of the instances — and they are rare among the lower forms of life — in which the maternal instinct is at fault.

Very obviously, then, before systematic work against yellow fever is begun in West Africa a survey must be made, to determine the limits there of both the normal and the compulsory breeding places of its yellow-fever vector, or vectors. If the compulsory breeding places should be beyond our control we must, by some of the methods just given, try to arrange for the control of normal breeding, so as not to induce compulsory breeding — remembering, always, that less than a 100% reduction of Stegomyia will eliminate yellow fever.

If the normal breeding habits of this mosquito in West Africa generally are those implied by the report of Horn and Tytler, and similar reports, as obtaining at Salt Pond and Secondee, the elimination of yellow fever from that region by the methods we have used in the Americas would be, I fear, impracticable.

DISCUSSION

Dr. A. E. Horn (Opening the Discussion). — After expressing his admiration for the invaluable work and the observations of Dr. Carter, in relation to the breeding places of mosquitoes, Dr. Horn said he desired to refer particularly to the point raised by Dr. Carter as to the breeding of Stegomyia mosquitoes in the Lagoon at Saltpond, on the Gold Coast, West Africa. The question, he said, is one of much importance, in view of the sporadic outbreaks of yellow fever in that neighborhood, and in consequence he had carefully examined the lagoon for Stegomyia larvae in 1904, and again to a less extent in 1920. There had been no success on either occasion, although there was little doubt that these larvae might occur in the refuse, tins, etc., occasionally to be found on the banks. Stegomyia had since been reported, however, from the Lagoon, and it was desirable that this body of water should be canalised or drained, in the interests of general

sanitation. He pointed out that the Stegomyia is a semi-domesticated mosquito occurring largely in and near dwelling houses and compounds. It was a matter of great and constant difficulty to keep these clear of mosquito-breeding facilities, said Dr. Horn, owing to the habits and customs of the local natives. He emphasized that it must be recognized that the keenest sanitary control of the natives and their dwelling places was necessary, and that the Stegomyia index of the town had to be carefully watched, before the Lagoon could be regarded as a compulsory breeding place.

Dr. Aristides Agramonte. — Dr. Agramonte said he would like to call attention to a means that has been employed, perhaps for the first time, in Santiago, Cuba, for eradicating the breeding places of mosquitoes under conditions that required the people to keep reservoirs. This method was to introduce into each of the various receptacles one or more fish of the varieties of Gambusiae (so-called millions) which destroy the larvae in such places. "The recommendation made by Dr. Carter," said Dr. Agramonte, "is one more example, in our experience, of what the intelligence of man can do in combating the mosquito. In this case the excellent results are to be expected, particularly for the reason that the intelligence and ingenuity employed are far superior to those of the ordinary man.

Dr. Carter (Closing the Discussion of His Paper). — Dr. Carter said that Dr. Horn had just informed him that he (Dr. Horn) had not found *Stegomyia aegypti* breeding in the Lagoon at Salt Pond or in the pools around it, although he had recommended the drainage of this Lagoon. "It was from this recommendation," said Dr. Carter, "and from the reference to the relation of such drainage to the occurrence of yellow fever at Salt Pond, that I inferred that Dr. Horn had found such breeding in and about this Lagoon and at Secondee. I am glad to know this. As I have said, we can, by a slight change of the methods we have used in the Americas, control Stegomyia production, and yet not induce them to form these unusual compulsory breeding places. By breeding *normally*, I mean, when there has been no interference in their usual breeding in artificial containers. If Stegomyia breed normally in ponds and puddles at Salt Pond and Secondee and if this is general in West Africa I do not see how their production could be controlled sufficiently to eliminate yellow fever, except at enormous expense. Methods whereby to do this could possibly be devised, but they are not now apparent to me, and I am extremely glad that my inference from the report of Drs. Horn and Tytler is not warranted by the facts, and that he does not have to meet this problem."

Dr. Carter quoted a letter from Dr. Carr, working at Parahyba do Norte — received the day of leaving Washington, D. C., — in regard to mosquito breeding in puddles. Dr. Carr stated he had not found this occurring in nature but he placed moist sand in a basin, packing it tightly against the sides of the basin, and dragging it up on the basin sides. Then he poured water on this slightly hollowed sand, so as nowhere to allow the basin to form any part of the water's edge. Captive Stegomyia, confined to this place, deposited eggs on the wet sand about a centimetre above the water. These developed larvae, which wriggled down to the water.

"I immediately wrote him to destroy all imagos thus produced, as this might be just the fillip needed to produce a strain that would breed in puddles in sand, instead of only in artificial containers. The example mentioned shows the adaptability of the mosquito under sufficient compulsion."

United Fruit Company Hospital at Almirante, Panama

THE "BLINDING FILARIA" OF GUATEMALA (ONCHOCERCA CÆCUTIENS, BRUMPT 1919)

FRIEDRICH FÜLLEBORN, M.D.

In the year 1915 Dr. Robles[1] found on the Pacific slopes of the volcanic ranges of Guatemala in a quite narrow strip of country, between 600 — 2,000 m. of altitude, many individuals, (in some places up to 97% of the population) on whose scalp were fibroma-like nodules about the size of a nut, containing a convolute of "*Filariæ.*" He associated them with certain chronic troubles of the eye (Keratitis, etc.) stating that the sight of people who had been practically blind for a long time was improved as if by a miracle in a few hours after the excision of the *filaria*-cysts. and cured in a few days. He also believes that the same parasite produces a certain type of erysipelas, known in the country as "*Erisipela de la Costa.*"

Later on, the ophthalmologist Dr. Pancheco Luna[2], Dr. Calderon[3], and other physicians of Guatemala[4], confirmed the splendid results arising from the excision of the "*filaria*-nodes" in a certain type of eye-diseases, formerly refractory to every other form of treatment. According to the publications, not only were the native Indians, but also white people — coffee planters of the infected region — successfully treated in the same manner. Mora[5] also reported a case of chronic mental disease apparently cured in ten days after the removal of a parasitic cyst of the occiput.

According to Brumpt[6], who investigated Robles' material, the nematode coiled up in the nodes, is an *Onchocerca* (reaching in the female the size of about half a meter) and so far as the morphology is concerned it is quite indistinguish-

[1] ROBLES, R., *Onchocercose* humaine au Guatémala produisant la cécité et "l'erisipèle du littoral" (*Erisipela de la Costa*). *Bull. Soc. Path. exot.* Vol. 12, 1919, No. 7 (With an appendix by Pancheco Luna and Brumpt).

[2] l.c. and PANCHECO LUNA, R. *La Juventud médica*, Guatemala, 1921. January, February, March and April.

[3] CALDERÓN, V. M., Contribución al estudio del *Filarido Onchocerca* sp. Dr. Robles 1915 y de las enfermedades que produce. Dissertation, Guatemala, 1920.

[4] ESTÉVES, P., CARLOS, *La Juventud médica*, Guatemala, July, August, September, 1921; SAÉNZ, CARLOS FLOTES, *Ibid.*, December, 1922.

[5] MORA, CARLOS FREDERICO, *Ibid.*, December, 1922.

[6] BRUMPT, l.c. *Bull. Soc. Path. exot.* 1919, No. 7.

able from the *Onchocerca volvulus* (R. Leukart) 1893 of tropical West-Africa. But considering the fact that the African form is found only *in about 1% on the scalp*, whereas by far the majority of the nodes of the *Onchocerca* from Guatemala are so located, he regards the latter not merely as a "biological variety" but as a new species, calling it *Onchocerca cæcutiens*, the blinding *Onchocerca*.

If we keep in mind the very close relationship between the African *Onchocerca* and the Guatemala-form, one would reasonably expect that the pathological effects of the two *Onchocercas* would also be similar.

The *Onchocerca volvulus* in many localities of tropical West Africa is so common that it affects nearly half of the population. We have known the affection for a long time, and it seems that usually the parasite gives rise only to quite harmless local, *fibroma*-like tumors, very rarely softening and suppurating. I do not think there is sufficient evidence that the African form also causes eye-troubles[1]; but on the other hand, according to the statements of Ouzilleau[2] and other French and Belgian authors[3], *Onchocerca volvulus* is apparently quite often the cause of changes in the lymphatic glands — where the *Volvulus-microfilaria* is said to be found nearly constantly — and also sometimes the cause of elephantiasis-like swellings of the skin, and of true *elephantiasis*. Further, the fact that the *Volvulus-microfilariæ* accumulate in very large numbers in the connective tissue of the skin, accounts for the view that *Volvulus* is also responsible for some other skin diseases of the West African negroes; but there is no agreement at all among the different authors concerning this question. Ouzilleau

[1]It is true, that Ouzilleau (Presse médicale, 14 Apr., 1923, No. 30. Ouzilleau, Laigret et Lefrou, *Bull. Soc. Path. exot.* Vol. 14, 1921, No. 10) is of the opinion that the *Onchocerca volvulus* of Africa can cause the same pathological changes of the eyes as those described by Robles. But with this exception — and a notice of Rodhain (*Bull. Soc. Path. exot.* Vol. 13, 1920, No. 10), that a European, for the last 8 years having a *volvulus*-nodule on his shoulder, complained "lately" of a diminution of vision — I find nothing in the literature concerning a bad effect of the *Onchocerca volvulus* with respect to the eyes: and because Ouzilleau found in carriers of *O. volvulus* — in addition to different kinds of skin affection, disturbances of nutrition, *arthritis*, epileptoid crisis etc.— also *Keratitis*, *Keratoconjunctivitis*, and *Iritis*, this does not follow, that there is also an *ætiological connection* between ailments of such different nature and the parasite, especially in a country where about *half of the population* is affected with the latter. I have only to remind you of the story of *Microfilaria perstans* and the sleeping sickness!

[2]OUZILLEAU, Ouzilleau, Laigret et Lefrou. l.c. p. 2.

[3]DUBOIS, *Bull. Soc. Path. exot.*, 1917, No. 4; RODHAIN, *Ibid.*, 1920, No. 10; MONTPELLIER ET LACROIX, *Ibid.*, 1922, No. 9.

and his collaborators (l. c.) have published that particular changes of the epidermis — what he calls "*Pseudo-Ichthyosis*", analogous to the "*Xérodermie sénile*"— and also other skin affections, are caused by the *Volvulus*, but he, as well as Brumpt and others[1], denies very positively the view of Montpellier and Lacroix[2] that the *Volvulus-microfilariæ* give rise also to the "*Gale filarienne,*" one of the symposium of clinically-similar skin diseases comprehended under the popular name "*Craw-Craw,*" an itching, papular and pustular skin affection very common among the West African negroes. A short time ago Macfie and Corson[3] confirmed the fact of the remarkable predilection of the *Volvulus-microfilariæ* for the connective tissue of the skin — stating that the *microfilariæ* creep out in great abundance from little pieces of skin, snipt with the scissors from the integument of the patients and then brought in 0.9 NaC—, but they could not find any ætiological connection between *O. volvulus* and skin affection; on the other hand, in the course of their investigations, the authors have discovered in Accra (Gold Coast) another species of *microfilaria* in the integument and they are inclined to think that this new *microfilaria*, the "*Agamofilaria streptocerca*" may perhaps be the cause of some of the skin affections attributed by Ouzilleau to the *Volvulus-microfilaria.*

You see, Gentlemen, that the connection between skin diseases and *Onchocerca volvulus* is not at all cleared up in a satisfactory manner!

Regarding the *Onchocerca* of Guatemala, there is nothing reported about "*Pseudo-Ichthyose*" or a *dermatitis* like "*Craw-Craw*" in connection with the parasites, and although I have given it my special attention, I have not seen such things in the skin of carriers of the *Onchocerca cæcutiens* in Guatemala.

But, as mentioned before, Robles brought the parasites in connection with the skin affection known in Guatemala as "*Erisipela de la Costa*" — according to him and other authors, frequently found and confined just to the *Oncho-*

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[1] BRUMPT, *Bull. Soc. Path. exot.*, 1920, No. 4 (discuss. of the paper of Montpellier et Lacroix); BRUMPT, *Ibid.*, 1920, No. 7; RODHAIN, *Ibid.*, 1920, No. 10.

[2] MONTPELLIER ET LACROIX, *Bull. Soc. Path. exot.*, 1920, No. 4 and 1922, No. 9; MONTPELLIER, DEGOUILLON ET LACROIX, *Ibid.*, 1920, No. 7 and 1921, No. 4.

[3] MACFIE and CORSON, *Ann. of Trop. Med. and Parasit.*, Vol. 16, 1922, No. 4, pp. 459–464 and 464–471.

cerca district. According to Robles' description (l. c.) the "*Erisipela de la Costa*" commences with the clinical picture customary for an acute febrile erysipelas, involving in the majority of cases only the face and the head, but in the chronic stage remains a hard, *elephantiasis*-like œdema of the skin, its surface being brilliant, pigmented and "eczematous" and presenting a special livid-greenish colour, which is quite characteristic for the affected parts.

Considering that the *Onchocerca volvulus* appears also to be connected with changes of the lymphatic glands and with elephantiasis, theoretically it would seem quite possible that, like *Filaria bancrofti*, the *Onchocerca* also could give rise to local obstruction of the lymphatic circulation[1] (being, in the Guatemala-form, confined especially to the head). According to the pathological-anatomical findings of Manson-Bahr on the one hand, and the remarkable therapeutical success of Rose, obtained in British Guiana with his *Vaccinetherapy* in the treatment of "*filarial lymphangitis*" on the other, one could hardly doubt that the latter is caused by *bacterial* infection, the *Filaria bancrofti*, being merely one of the many causes giving rise to it through lymphatic obstruction, and thereby lowering the resistance of the tissue to a predisposition for bacterial invasion, the *bacteria* in turn causing the *lymphangitis* and later on the *elephantiasis*.

On the other hand, it does not seem impossible that the *microfilariæ* of *Onchocerca*, as well as the *microfilariæ* of *Volvulus* (those of the Guatemala-form very probably will be found to be numerous in the connective tissue of the integumentum[2]) could cause also *directly* a swelling of

[1] If the *Onchocerca* develops in the lymphatic vessels — which seems to be quite possible — there could surely result a good deal of lymphatic obstruction; because, in addition to the bigger nodes, accessible to palpation, there may be very often much more numerous smaller ones that clinically cannot be diagnosed at all. (cf. Fülleborn and Simon, *Archiv. f. Schiffs- u. Trop. -Hyg.* 1913, *Beiheft* 9, footnote to p. 17.)

[2] I had the opportunity of visiting Guatemala City with the other members of the Kingston Medical Conference and was able to demonstrate the *Cœutiens-microfilariæ* in greatest abundance in pieces of skin taken from the ear and the scalp of a *cœutiens*-carrier, using the technique of Macfie and Corson already mentioned.

Perhaps they accumulate also in the cornea or other parts of the eye. On this occasion I saw 3 *cœutiens* cases selected and brought to the city by Dr. Zschukke. All 3 cases were suffering from severe photophobia; one of them showed a marked diffuse interstitial *keratitis* of the whole cornea, and the acuity of vision, when objectively tested, was highly diminished. The parasitic nodules of the scalp (and one from the body) were excised in all 3 patients by Dr. Zschukke and Dr. Estéves, but I cannot judge at present the therapeutic effects of the operation in these cases, owing to the fact that I had to leave the town 2 days after.

the skin, perhaps through a *toxic* effect, in a manner analogous to the way that *Loa loa* apparently gives rise to the "*Calabar Swellings*[1];" indeed, the latter runs a course without any fever!

However, Pastor Guerero[2] along with other physicians of Guatemala, thinks that "*Erisipela de la Costa*" is *myxœdema* of the skin, pointing out that there is a region on the slopes above the district affected with "*Erisipela de la Costa*" (and also with *Onchocerca cœcutiens*), where goitre is endemic.

I cannot here discuss the question in detail and will give only some remarks about my personal experiences in Guatemala. Within the few days during which together with Dr. Zsuchukke—a former student of our School of Tropical Medicine in Hamburg — I could study the *Onchocerca* question on a coffee-plantation, where about 70% of the native Indian laborers were "carriers" of the Onchocerca[3], we have not seen cases of the acute febrile stage of the "*Erisipela de la Costa*," as described and illustrated by Robles and Calderón (l.c.). If we leave out of account some doubtful cases, only 2 persons, who were also carriers of *Onchocerca*, presented some hard œdema of the face (causing in one of them a distinct diminution of the eye-opening); and in spite of the fact that there was no perceptible greenish coloration of the skin, we were told by the natives that these 2 persons were suffering from "*Erisipela de la Costa.*"

On another occasion we saw in Guatemala City a young German coffee-planter (living in the Onchocerca district, but without palpable *Onchocerca* cysts on his body) who was affected by a very intensive œdema of his whole left arm. The hard swelling that had commenced about 2 weeks previously on the dorsum of the hand, caused some pain in consequence of the strong tension of the skin, but there was not the slightest trace of inflammation, *lymphangitis* or *lymphadenitis;* there was no redness of the skin

[1] CALDERÓN (l.c. pp. 40–41) also thinks that there is a connection between Erysipelas and the *Cœcutiens-microfilariæ.*

[2] PASTOR GUERERO, *La Juventud médica,* Guatemala, 1921, July, August, September; 1922 September.

[3] It was in the plantation "Olas de Moca" (near the lake of Amatitlan) where we had a hospitable reception from its administrator Mr. Brückner. 70% *Onchocerca*-carriers is also the *highest* rate mentioned by Calderón (l.c., p. 20) for infected plantations!

and no fever, and the patient felt perfectly well. About 2 weeks later the limb was quite normal and there was no relapse, as he told me when I saw him again in Hamburg a year and a half later. The gentleman told us that many of the laborers of his plantation also suffered "off and on" from similar swellings.

Further, I had the opportunity of seeing in Hamburg a 5-year-old boy from Mexico who had, on an otherwise normal but slightly thickened skin of the face, a bluish-green spot on the right cheek about 3-4 cm in size.[1]

The father, a German coffee-planter, from a district near the Guatemala border (Valle de Custipec, between Concordia and Mapaslipec about 800 to 1,400 m. high) asserted that in his locality almost all the children of Europeans, and still more frequently those of the native Indians, suffered periodically from intensive swellings of the face and arms, running a course apparently free from fever, and known in the country as "Erisipela." Later on the skin of the children's faces turned bluish like that of our little patient; (this had nothing to do with "*Mal de Pinto*," with which he was quite familiar[2]). He had not noticed this discoloration among the grown-up Indians, but only a slight skin thickening of the face, especially on the eyelids. On the other hand, about ⅓ of the Indians of the same region showed nodules on the scalp. Even a 3½ year old child of his own — suffering also from the swellings, with incipient bluish coloration of the face—was affected with 2 such nodules about the size of a "coffee-berry" (we did not notice this in our Hamburg patient). Goitre is also endemic in the same district.

Although I have not up to now examined nodule-material from Mexico for *Onchocerca*, it appears to me quite possible that there, also, the "*Erisipela*" and the *Onchocerca* may be endemic in the *same district*, but surely this is not sufficient to prove that the "*Erisipela*" is caused also by the

[1] FÜLLEBORN, *Archiv. f. Schiffs- und Tropenhygiene*, 1923, S. 386–390.

[2] The bluish coloration of our patient's cheek reminds me of an affection that I had seen in Bogotá, known in Colombia as "*Carate*" and identified usually with "*Mal de Pinto*" (Pinta), although the discoloured skin in the "carate" of Colombia is dry, and not wet and stinking, as the textbooks describe the "*Pinta*" (cf. Luis Cuervo Márquez, "Geografia médica y Pathologica de Colombia, Bogotá"—Nueva York, 1915).

parasite[1]). In this connection it may be mentioned, that, according to Chagas, there is in children infected by Schizotrypanum cruzi also a swelling of the face resembling Myxœdema; that on the other hand Schizotrypanum is not absent from Central-America is proved by the findings of Dr. Segovia of Salvador.

Of still greater interest, as to the connection between *Onchocerca cœcutiens* and the "*Erisipela de la Costa*," is the question about the parasite and eye-disturbances, the latter, as stated by Robles, setting in simultaneously with the Erysipelas of the face. According to the publications, the first stage of the eye-troubles begins with pain in the affected eyes, headache, severe photophobia, "feeling of foreign body," *conjunctivitis*, and a diminution of vision. A peculiar superficial *Keratitis punctata* of the palpebral fissure is said to be especially characteristic of the disease. The later stages show acute and chronic *Iritis*, which leads finally to adhesion, thereby giving rise to "a deviation of the pupil downwards, not found in any other eye-diseases,"[2] and also to complete blindness; the *fundus oculi* remains in ordinary cases apparently unaltered. Also reported as characteristic is *microcornea*, i.e. a diminution of the transparent corneal margin in consequence of circular *Keratitis*. In other cases of disturbance of vision, sometimes of a very high degree (and of other subjective symptoms such as photophobia, etc.), healed after excision of the node, *objectively* eye-changes could hardly be determined.

Calderón (l.c. pp. 103–104) points out that every one who has *Onchocerca*-cysts on his head also suffers in regard to his vision but that the eye-ailments caused by *Onchocerca*, except cases with too advanced cicatrization, are curable by excision of the nodes, and even the latter show improvement of vision and decrease of photophobia. More than a thousand-and-some-hundreds of cases have been operated upon — the most by Robles, Pancheco Luna and Calderón — and Calderón mentions in his paper (l.c.) many histories of patients successfully operated upon.

[1] It may be mentioned here that Rodhain (l.c.) remarked that a 3-year-old negro child of the Congo-basin, which had an *Onchocerca* node on the occiput (a very rare exception in Africa) was suffering at the same time from a face swelling, and that after the excision of the node the swelling disappeared. The mother had asserted that the former was the cause of the child's trouble.

[2] CALDERÓN (l.c., p. 104) writes "La desviación de la pupila hacia abajo es desmasiado típica porque no hay otra enfermedad de ojos que la presente."

It may be mentioned that Pastor Guerero, although sceptical regarding the ætiological influence of the *Onchocerca*, admits freely that in spite of some failures the removal of the parasite-cysts was often followed, either immediately or after some days,[1] by a favorable effect regarding the vision, but he remarks that the patients were very seldom examined later on to determine whether or not the cure was permanent, and there were not sufficient statistics to enable one to arrive at any definite conclusions. On the other hand Calderón (l.c. p. 63) points out that 45 cases operated on 3 years ago were under control and found to be healed permanently.

Robles and Calderón believe that the eye-affections are provoked by *Onchocerca-toxins* and that the latter are eliminated by the excision of the parasitic nodes; while Pastor Guerero holds it to be improbable that the hypothetical toxins accumulated for years in the body could be eliminated within the few hours that elapsed between the operation and the improvement of the vision, and he considers it more probable that the operation may perhaps remove a pressure on a nerve which was causing the eye-trouble.[2]

But this explanation of Pastor Guerero is hardly acceptable, and Robles in favour of his toxin-hypothesis can put forward the observation that, after the removal of an *Onchocerca-cyst* located in an unusual place — i.e. *not on the scalp but on the hip* — he could ascertain an improvement already evident the next morning.

So far as I know, there is in the whole range of parasitology nothing analogous to the experiences reported from Guatemala regarding the effect of *Onchocerca* on the eyes. It would be quite interesting to determine whether the *Cœcutiens-microfilariæ* accumulate also in the tissues of the eye!*

Concerning the personal experiences of Dr. Zschukke and myself in the *Onchocerca* territory, the following is worthy of note: Of 12 more thoroughly examined adult, native *Onchocerca*-carriers, 2 complained about their eyes,

[1] Some colleagues told us that there were cases in which the improvement of the vision was evident only after a week or more.

[2] Also the surgical operation *by itself* — causing sometimes a good deal of local reaction — may in the sense of "derivative therapy," "counter-irritation" ("ableitende Therapie") produce a certain favourable effect on the eye, although hardly sufficient for a *permanent* cure.

*See footnote 2, p. 244.

but tested with an improvised "Snell's table for analphabetics"[1] they showed "normal acuity of vision"; and of a number of other eye-sufferers who came to us hoping to be cured, only 2 had a marked defect of vision.

1. One of them whose right eye had "normal," but the left only about a "half" acuity of vision (otherwise nothing more being perceptible than a conjunctivitis) declared that since a year ago he had periodically had a diminution of vision. On the head there was a small node, but he told us that formerly there was a bigger one which had about a year ago spontaneously disappeared. The patient, who was treated with intravenous injections of Stibenyl, could not be further observed.
2. The second case was an Indian, whose acuity of vision also objectively showed some diminution. Dr. Zschukke surgically removed an *Onchocerca* node from his scalp, and when he saw the patient 3 to 4 weeks later, the latter told him that 8 days after the operation he had observed a progressing amelioration of his vision so "that he was able again to shoot birds." Objectively the power of vision seemed also to be improved a little. If "auto-suggestion" could be excluded, this could be regarded perhaps as some indication of the success of the excision of the parasitic node.

Except for these two cases, some of the people who said to us that their vision was altered (but, tested by Snell's tables, showed "full acuity of vision") complained of *photophobia*, burning of the eyes, etc.; and sometimes there was also more or less conjunctivitis. But eye-troubles of such kind are not confined to the *Onchocerca* district, being quite frequently found also in other places; and likewise we saw decided cases of "*microcornea*," not only in some of our *Onchocerca*-carriers, but also in laborers of plantations situated outside of the *Onchocerca*-district. The superficial

[1] It is true that primitive men (and also a good many white people) often have *more* than "normal" acuity of vision, and therefore it may be that also in these 2 cases there was a certain diminution of sight as compared with formerly, the Indians being apparently remarkably sensitive against even small differences in sharpness of vision.

Keratitis punctata of the palpebral fissure, regarded as especially characteristic of the *Onchocerciasis* of the eye, we have not seen. Furthermore, changes of the iris and of the pupil were not evident in our cases from the *Onchocerca* region; but indeed, neither Dr. Zschukke nor I am an eye-specialist.

Therefore we were not in a position to confirm a connection between *Onchocerca cœcutiens* and eye-affections; but this does not mean that we should in any way doubt the statements of colleagues who have far richer experience at their disposal than we have. A friendly proposition from Dr. Calderón to show us the favourable effects of the extirpation of the *Onchocerca*-cysts on eye-trouble, to our greatest regret did not materialise.

On the other hand, however, we have the impression that the predominant majority of *Onchocerca cœcutiens*-carriers, like the *Volvulus*-carriers of West Africa, are thoroughly healthy individuals and that in the part of the *Onchocerca*-district visited by us (although one of the most infected) only a relatively small percentage of the people apparently suffer from serious eye-disturbances. Also, if one admits that the latter are caused by *Onchocerca cœcutiens* and are healed by its removal, it does not on this account seem to us to be necessary, as was proposed, that *all the plantation-laborers* who are *Onchocerca*-carriers, should, for the sake of *prophylaxis*, have the nodes excised, especially when the authors agree that in already chronic cases with severe visual defect the operation is still in time to restore it!

As the surgical removal of the node (carried out under local anæsthetics) is not always quite simple, we have attempted to kill the parasite within the node, through injection of medicaments — technically much more simple than the excision. Injection of cocain in the nodes, with the hypodermic syringe, seemed to have been effective in *one* of 2 cases, inasmuch as when the nodes treated in this manner were excised 3 or 4 weeks later by Dr. Zschukke, the *microfilariæ* in one of the nodes were found to be dead, but still alive in the other. It would be necessary to repeat these attempts on a bigger scale, and also to try other preparations (e.g., carbolic acid, antimony preparations, ether, emetine, etc.) before one could judge of the efficacy of the procedure.

Intravenous injections with *Stibenyl* and *Tartarus stibiatus*, at least by the limited dosage used by us, was not a success at all, the nodes when excised later on containing living *microfilariæ*. The intravenous treatment would have, if effective, the great advantage that it could attack also the small impalpable nodes and at the same time the *microfilariæ;* but indeed, after the experiences of O'Connor[1] with *Filaria bancrofti*, there is only little hope left that intravenous injections will be successful in filarial diseases!

It may be mentioned that the parasites do die spontaneously inside the nodes, the latter softening and probably later being absorbed; also, we are told that an Indian, mechanically squashing a node on his head with a stone, found later that the node had disappeared.

Morphological differences between *Onchocerca volvulus* and *Onchocerca cœcutiens* we (as well as Brumpt and others) could not find. Also the *microfilariæ* of both parasites (resembling in general appearance the *microfilaria bancrofti* but without a sheath) do not show differences regarding the details of the anatomical structure and the position of the organs in relation to the total length. The details of the measurements will be published later.

It was reported in the literature that the *microfilariæ cœcutiens* were not present in the blood, but we could demonstrate them not only in blood-preparations taken in the usual manner from the patient's ear-lobe, but also in blood gained by venepuncture.[2] On the other hand it seems to be very probable that the *microfilariæ cœcutiens* behave in the same manner as those of *Volvulus* — i.e. being scanty in the blood, but accumulating in great numbers in the connective tissue of the skin.

The accumulation of the *microfilariæ* in the tissue of the skin seems to indicate that the transmitters of the *Onchocerca*, not known at present, may be arthropods sucking not only blood, but also the juice of the tissues. The epidemiological statements of Robles make it probable that the transmitters of *Onchocerca cœcutiens* were sucking *only*

[1] O'CONNOR, "Research in the Western Pacific." *Research Mem.* of the London School of Tropical Medicine, Vol. 4 (1923).

[2] About *microfilaria volvulus* in the blood-preparations, see FÜLLEBORN and SIMON (l.c.); in the blood of venepuncture, see CORSON, "Annals of Tropical Medicine and Parasitology", Vol. 16 (1922), No. 4, pp. 407–420.

during daytime, and he suspects that they are a species of *Simulium* — "Coffee-flies." (For *Onchocerca gibsoni* of the Australian cattle there seems to be some indication that they are transmitted by *Tabanidæ*.[1])

I think, Gentlemen, you will agree with me that the question of *Onchocerca cæcutiens* is very interesting, but that a good deal more investigation is necessary before we arrive at definite and final conclusions.

SUMMARY

1. A connection between *Onchocerca volvulus* of West Africa and eye-diseases, seems to be not sufficiently proved; but on the other hand, it appears that the parasite can cause changes of the lymphatic glands, *elephantiasis*-like swellings of the skin, and real *elephantiasis*. That the remarkable accumulation of the *Volvulus-microfilariæ* in the connective tissue of the skin can give rise to other skin diseases — "*Pseudoichthyosis*" etc. according to Ouzilleau; "*Gale filarienne*" (Craw-Craw) according to Degouillon et Lacroix — is still a matter of controversy.

2. The *Onchocerca cæcutiens* (confined to an altitude of 600 — 2,000 m. in a narrow strip of country situated on the Pacific slopes of the volcanic ranges of Guatemala) is, regarding the morphology, indistinguishable from *O. volvulus* of West Africa, but the nodes containing the coiled-up parasites are nearly always located on the scalp only, whereas *Volvulus* is very rarely so found. In the infected region, more than half of the population can be carriers of *Onchocerca cæcutiens*.

Skin affections like "*Pseudoichthyosis*" or "*Gale filarienne*" do not seem to be caused by *O. cæcutiens*, but Robles, the discoverer of the parasite, brings it in connection with the "*Erisipela de la Costa*" confined just to the *Onchocerca* district. According to Robles the "*Erisipela de la Costa*" begins as an acute febrile erysipelas, restricted usually to the face and head, in its chronic stage leaving a hard swelling of the skin characterised by a livid-greenish coloration. Pastor Guerero thinks that the affection is *myxœdema*.

It seems quite possible that an obstruction of lymphatic vessels in *Onchocerca* infection (as in *Filaria bancrofti*) would

[1] CILENTO, "Med. Jour. Australia." 10th Year, 1. No. 16, Sidney, 21st April, 1923 (ref. *Rev. appl. Entomology*, August, 1923).

cause a predisposition of the tissue for bacterial invasion inducing *Erysipelas*. On the other hand the *Cœcutiens-microfilariæ* — like those of *Volvulus*, accumulating also in the connective tissue of the skin—could give rise, possibly through a toxic effect, to swellings of the skin, as does apparently the *Loa* in the case of "Calabar-swellings."*

3. Fülleborn in collaboration with Dr. Zschukke, studying for some days the *Onchocerca* question on a plantation where about 70% of the native Indian laborers were carriers of the parasite, had not the opportunity to see a case of the acute febrile "*Erisipela de la Costa*," but only 2 cases of a light chronic swelling of the face in carriers of *cœcutiens*-nodes in which there was not a greenish coloration of the skin.

Furthermore, in Guatemala City we saw a German coffee-planter of the *Onchocerca*-district (though not presenting palpable *Onchocerca*-nodes) suffering for a month from a very intensive swelling of the whole left arm, but without fever and without the slightest sign of *lymphangitis* or any other inflammations (later on the affected limb became quite normal). He told us that his native laborers suffered "off and on" from similar swellings.

4. Fülleborn also saw in Hamburg a 5-year-old boy from Mexico, presenting on an otherwise normal but slightly thickened skin of the face, a bluish-green big spot on the right cheek; and the father of the child, a German coffee-planter from the "Valle de Custipec" (between Concordia and Mapaslipec, near the boundary of Guatemala) told him that there almost all the children suffered periodically from intensive swellings of face and arms, running a course apparently free from fever, and known in the country as "*Erisipela*"; later on the skin of the face turned bluish, like the face of the above-mentioned 5-year-old patient (reminding Fülleborn of the blue "*Carate*" of Colombia but, according to the child's father, it was not "*Mal de Pinto*," with which he is quite familiar). He had not noticed this discoloration among the grown-up Indians, but only a slight thickening of the face, especially on the eyelids. However, about ⅓ of them had nodes on the scalp. Even a 3½ year old child of his own — suffering also from the swellings, with incipient bluish coloration of the face — was

*See footnote 2, p. 244.

affected with 2 such nodules on the head, about the size of a "coffee-berry" (we did not notice this on our Hamburg patient). It seems, therefore, that also in Mexico there is an *Onchocerca*-district, where swellings of the skin, followed by a bluish-green discoloration but running a feverless course, are very common. Perhaps the *Cœcutiens* may have a still wider distribution. On the other hand, according to Chagas, there is in children infected by Schizotrypanum cruzi also a swelling of the face resembling Myxœdema (that Schizotrypanum cruzi is not absent from Central-America is proved by Dr. Segovia of Salvador).

5. Robles and others have stated that the carriers of *Onchocerca cœcutiens* suffer frequently from a specific eye-disease, curable within a few days or hours through the excision of the *Onchocerca*-cysts. Fülleborn and Zschukke had not the opportunity of seeing cases which confirm a clear connection between eye-troubles and the *Onchocerca*, although they are far from doubting the statements of colleagues who have much wider experiences at their disposal. In spite of the fact that about 70% of the laborers of the plantation where they were studying the question, were *Onchocerca*-carriers, only 2 of their patients had, objectively tested, an appreciable degree of diminution of vision. Superficial *Keratitis punctata* of the palpebral fissure — regarded as especially characteristic for the *Onchocerciasis* of the eye — they have not seen; nor the *Iritis* of the *chronic Onchocerciasis*. On the other hand, circular marginal *Keratitis* and *conjunctivitis* with subjective symptoms such as *photophobia*, etc.— as they are described for the eye-*onchocerciasis* — are not infrequently found also *outside* of the *Onchocerca*-district.*

The *Cœcutiens*-carriers seen by us seemed to be perfectly healthy individuals and, although one admits that the *Onchocerca* can give rise to eye-troubles, the proposed *prophylactic* removal of the nodes of *all affected people* does not seem necessary, especially when the authors agree that in already chronic cases with severe visual defects, the operation will still restore the vision.

6. Some attempts to substitute the surgical removal of the nodes by the more simple technique of Cocain-injection into the parasitic cysts, did not give a clear result regarding

*See footnote 2, p. 244.

the death of the parasite, but it would seem recommendable to repeat it on a bigger scale, and also with other preparations (carbolic acid, antimony-preparations, ether, emetin, etc.). Intravenous injection with antimony-preparations apparently did not influence the parasites.

7. Morphological differences between *O. volvulus* and *O. cæcutiens* could not be established by us; nor differences in the anatomical details of the *microfilariæ*.

8. The *microfilariæ* of *O. cæcutiens* could be found by us in the blood taken in the usual manner from the patient's ear-lobe, and also in the blood obtained by venepuncture; but it could be proved that they accumulate in immense quantities especially in the connective tissue of the skin, as in the case of the *Onchocerca volvulus*.

9. The transmitters of the *Onchocerca* may be arthropods, sucking not only blood, but also the juice of the tissues. The epidemiological statements of Robles make it probable that in the case of *Cæcutiens* the transmitter is feeding only during the daytime; Robles thinks it may be a species of *Simulium* —"coffee-flies."

DISCUSSION

Dr. Aldo Castellani (*Opening the Discussion*).— We have been listening to a most interesting paper, a paper written by an expert.

I have not yet had personal experience of *Onchocerca* in America, but I have seen this condition in Africa, and in a general way I am in complete agreement with Professor Fülleborn. As regards *Craw-Craw*, I quite agree with Professor Fülleborn that the term has been applied to different skin conditions. In a number of cases the so-called *Craw-Craw* is merely "scabies." In many other cases you will find *Trichophytons* and *Epidermophytons*. Finally, you find cases in which no organism of any kind has been discovered, and to these cases Daniels and I have applied the term: "coolie itch."

I am interested in what Professor Fülleborn said about the juxto-articular nodules. There is no doubt that in certain cases *Onchocerca* may produce nodules near the articulations which are clinically practically identical to what we call juxto-articular nodules. However, in what I consider to be true juxto-articular nodules, the examination for *filariæ* is negative.

I am very much interested in the treatment of *Onchocerca* and of filarial conditions in general. I quite agree with Professor Fülleborn, that as yet no treatment has been found which will kill the *microfilariæ* in the blood. Salvarsan, neosalvarsan, tartar

emetic and many other drugs have been tried, but in my experience the results have always been very poor or completely negative.

Dr. José Azurdia.— I will say only a few words about the disease which Dr. Fülleborn found in my country. The principal point, I think, about the disease — in connection with the explanation made by Dr. Fülleborn, who has been there and studied the matter — is the question of a particular blindness that we have there, among the carriers of this parasite. Dr. Fülleborn believes that it is only a question of suggestion in the minds of the natives, and of the doctors also. It may be so in some cases, but blindness really exists, and consists of *keratitis punctata* and *iritis*. Many of the sufferers become completely blind after they have suffered a long time from the disease. When it is possible to perform an operation at the beginning, the way Dr. Fülleborn has explained, that condition of the eye is absolutely cured. In Guatemala we have a committee in the district which Dr. Fülleborn has spoken of, to treat the disease in the way I have explained; and the only way to cure the disease is the surgical treatment to take out the nodules with the parasite.

Now the question is how to be quite sure about the cause of the blindness. Is it a *toxemia?* It may be, but as stated by Dr. Fülleborn, he had found this *filaria* in the circulation of the blood, so that it is not certain what is the cause of the blindness. There is a doctor working under the Department of Health, who is performing every day from 200 to 600 operations and removing the parasites from the nodules, and the patients all recover.

Dr. Friedrich Fülleborn (*Closing the Discussion of his own Paper*). — I wish to thank Dr. Castellani for his friendly remarks. What I did say about the resemblance of *Onchocerca* nodules to the tumor *juxto-articulosis*, referred only to the clinical resemblance because the 2 conditions are certainly quite different etiologically.

Also, I am very thankful to Dr. Azurdia for his remarks, because they give me an opportunity to avoid a mistake which may have been caused by my bad English. If I did say that maybe, in some cases which seemed to improve after the excision of the *Onchocerca* nodes, it would not be easy to exclude auto-suggestion, I surely did not mean that auto-suggestion could play a part in the reported cases of practically blind people who had recovered a few days after the excision of the nodes; and you will remember that I have pointed out that coffee-planters, and not only native laborers, were treated successfully by this method in cases formerly refractory to every other form of treatment.

From these cases it seems to be clear that there must be some connection between the improvement of the vision and the excision of the nodes, although the nature of this connection is difficult to understand.

"BAYER 205" IN *FILARIASIS*

F. G. Rose, M.B.

(*Read by Title*)

In 1923, through the kindness of Dr. G. C. Low, I obtained from Dr. C. R. Hennings, of Messrs. Bayer & Co., Hamburg, a limited supply of the drug "Bayer 205," in order to study its effects on filarial worms.

As some of the capsules were broken in transit, I received only about 30 grammes, so that I deemed it best to use the bulk of the supply in experiments *in vivo* with *Filaria bancrofti*.

The following is an account of the results of the administration of the drug to infected patients, as judged by repeated counts of the embryos in the cutaneous night-blood.

Preliminary

"Bayer 205" is described by Low and Manson-Bahr[1] as a whitish powder, readily soluble in distilled water, to which it imparts a pinkish tint. They state, moreover, that no local reaction follows its escape into the subcutaneous tissues, and that 2 grammes may be given at a time without disturbance.

The substance supplied to me, however, was a light-brown powder, 1 gramme of which dissolved with some difficulty in 10 cc. of distilled water; before solution took place, a gelatinous mass was formed, which slowly dissolved on shaking; the solution acquired a brownish-yellow tint.

A somewhat painful local reaction, which took some days to subside, on one occasion followed the escape of a small quantity into the subcutaneous tissues.

The administration of 2 grammes in 1 dose, on 1 occasion, to a man who had a week before received 1 gramme intravenously, resulted in a violent reaction, characterized by a rigor and *pyrexia* lasting over 4 hours, leaving him prostrate so that he was unable to resume work for 48 hours after the administration of the drug.

[1] Low and Manson-Bahr; "Transactions of the Royal Society of Tropical Medicine and Hygiene," Vol. 16, No. 7, Jan. 18, 1923, p. 340.

I think it right to state these remarkable differences, without attempting to suggest an explanation.

METHOD OF ADMINISTRATION AND DOSAGE

In every case the intravenous method was used, and the dose consisted of 1 gramme dissolved in about 10 cc. of sterilized-rain or distilled water.

Local or general reactions occurred in 3 cases, 2 already described as resulting from the escape of a small quantity of the solution into the subcutaneous tissues and from the administration of a 2-gramme dose, and the 3rd occurring after a dose of 1 gramme, and characterized by fever, diarrhoea and peeling of the hands and feet; 6 cases, numbered 1, 2, 3, 4, 9 and 10, received the drug, but of these only Nos. 4 and 10 received a full course of 10 grammes.

No. 1 received 4 grammes; No. 2, 3 grammes of "Bayer 205" and 0.15 gramme of Tartar Emetic in 2 doses; No. 3, 5 grammes of "Bayer 205" and 0.1 gramme of Tartar Emetic; and No. 9, 2 grammes of "Bayer 205." All these individuals neglected to return for counts or for further injections.

There were 4 cases, Nos. 5, 6, 7 and 11, which were used as controls, No. 7 receiving 1.5 grammes of Tartar Emetic in 10 doses, while the others received no treatment.

The courses of "Bayer 205" were given as advised by Low and Manson-Bahr[1], namely, 3 doses of 1 gramme at close intervals, followed by 1 gramme weekly up to 10 grammes — Antimony Potassium Tartrate was administered in Case No. 7, as prescribed in Byam and Archibald's "Practice of Medicine in the Tropics,"[2] in a freshly prepared 6% solution in sterilized water.

EXAMINATION OF THE URINE

The urine was examined in every case before the injections were commenced, and after almost every injection.

Frequently the injections were followed by the appearance of albumin only, or of albumin and granular and hyaline casts. These conditions invariably disappeared after about 24 hours.

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[1] LOW and MANSON-BAHR; *loc. cit.*

[2] BYAM and ARCHIBALD; "Practice of Medicine in the Tropics," 1st Ed., Vol. 3, p. 1,742.

Counting the Embryos

I am aware that there are many pitfalls in the method of estimating the effect of a drug on the parent worm by means of repeated, even daily, counts of the embryos in the peripheral night-blood.

In the first place, as Sir Leonard Rogers pointed out[1], in a preliminary report on the effects of Tartar Emetic, the estimates of the length of life of the embryos varied from a number of months — according to Bancroft — to a year or more, as Sir Patrick Manson thought probable, or even longer according to D. R. Croll[2], so that observations, to be of value, would have to be conducted over very long periods.

Fülleborn[3] found that the embryos of *Filaria immitis* could live for at least 10 months in the circulating blood of the dog.

The cases here under review have been under observation since the injections were commenced, for periods ranging only from 2 to 5 months, though 2 have been under observation for 2–3 years prior to the use of "Bayer 205."

Secondly, in infected areas there is the possibility of reinfection, which might produce anomalous results.

Although the period of incubation is not accurately known, Anderson[4] reports finding embryos present in a child of 14 months; this, I think, is the youngest case reported, so that this period is probably a fairly long one.

All the patients were carefully instructed as to the use of mosquito netting, and the advisability of killing all the blood-gorged mosquitoes encountered.

Moreover, the infections were heavy, and, as Manson-Bahr[5] and Cruickshank and Wright[6] have shown in the case of *Stegomyia pseudo-scutellaris* and *Culex fatigans*, respectively, a heavy infection tends to kill the infected mosquito.

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[1] Rogers; *The Lancet*, Oct. 4, 1919, pp. 604 et seq.

[2] Croll; *British Medical Journal*, Jan. 4, 1919, p. 28; *cit.* Rogers, *loc. cit.*

[3] Fülleborn; "Beiheft Archiv. für Schiff-und-Tropenhyg." (8) Nov. 1908, *cit.* Manson-Bahr, "Filariasis and Elephantiasis in Fiji," p. 15.

[4] Anderson and others; "London School of Tropical Medicine; Research Memoir Series," Vol. 5, 1924, Memoir 7, "Filariasis in British Guiana," p. 113.

[5] Manson-Bahr; *cit.* Byam and Archibald, *loc. cit.*, Vol. 3, p. 1,911.

[6] Cruickshank and Wright; *loc. cit.*

Thirdly, certain conditions, such as fever, are known to interfere with the periodicity of the embryos, so that counts taken at the same time on separate occasions may not be strictly comparable.

Periods of *pyrexia*, where they occurred, have therefore been avoided in the series of counts here given.

Fourthly, if such small quantities as 20 cmm. or less are taken, it has been shown by Manson-Bahr[1] that error may be introduced because of the absence of uniform distribution of the embryos in the peripheral blood, so that one slide made from 16 cmm. of blood may contain even 3 times as many embryos as another made, from the same quantity of blood, at the same time, from the same individual. When comparatively light infections are being dealt with, such counts may be very misleading.

Suganuma[2] uses 1 cc. of blood mixed with 100 cc. of a 3.5% acetic-acid solution and 10 cc. of acetic acid saturated with Fuchsin and centrifugalized.

I have found that using 200 cmm. of blood collected in an Ostwald's pipette, where the infection is a heavy one, the error is not a serious one, though even this quantity is too small in dealing with light infections.

In all these cases 200 cmm. of blood were taken, spread on 3 slides, allowed to dry over-night and then dehaemoglobinized by means of distilled water and counted, while still wet, under the ⅔ lens of the microscope.

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[1] Manson-Bahr; "Filariasis and Elephantiasis in Fiji," p. 83.

[2] Suganuma; *International Med. News*, Aug., 1921, No. 994; *cit. Tropical Diseases Bulletin*, Vol. 19, No. 8, p. 654.

Counts of Embryos in Peripheral Night-Blood (9 p.m. With a Few Exceptions; Not Later Than 9.30 p.m.) During and After Administration of "Bayer 205"

Case 1. Black, male, 36; *lymphadenitis*, right groin; fever. Had been confined to bed 3 days.

Preliminary Count

Time	No. in 1 cc. of cutaneous blood	No. of embryos in 1 cc. of venous blood
11 a.m.	450	155
3 p.m.	30	...
7 p.m.	20	...
11 p.m.	565	...
7 a.m.	160	...

After Treatment

Day	No. in 1 cc. peripheral night-blood (9 p.m.)	"Bayer 205"
1	...	1 gramme
8	...	1 gramme
10	760	1 gramme

After the last injection, this patient was not seen for 3 months, the reason being, according to his account, that he was very ill for 3 days after, with fever and diarrhoea. His hands and feet peeled, the whole sole of each foot being cast off, and he was not himself again for 3 weeks.

His cutaneous blood contained (at the end of 3 months) at 9 p.m. 995 embryos in 1 cc.

Case 2. Portuguese, male, 50; in good health; had had no attacks for about 2 years. Embryos 2 — 3,000 per cc. at 9 p.m. for 2 years, in blood taken at intervals. In the week before treatment he gave counts of 3,105 and 2,505 per cc. on 2 occasions.

After Treatment

Day	No. per cc. 9 P.M.	"Bayer 205"	Tartar Emetic
1	3,755	1 gramme	...
5	5,270	...	...
8	1,550	2 grammes (violent general reaction)	...
10	3,200	...	...
12	1,860	...	...
20	690	...	...
22	3,400	...	...
26	2,600	...	...
30	2,625	...	...
115	565	...	...
128	2,000	...	0.1 gramme
132	4,000	...	0.05 gramme
156	3,330	...	...

Case 3. Mixed race, male, 25; just recovered from an attack of acute *orchitis;* 3 years ago he had had 10 — 11,000 embryos per cc., this number falling temporarily to 3,350 after injections of a colloidal preparation of Arsenic.

Just before treatment his count was as follows: —

Time	Embryos in cutaneous blood
11 A.M.	250
1 P.M.	87
5 P.M.	115
9.30 P.M.	5,750

During and After Treatment

Day	No. per cc.	"Bayer 205"	Tartar Emetic
1	5,750	1 gramme	...
2	...	1 gramme	...
3	4,650	1 gramme	...
4	10,560	...	...
6	6,745	...	...
8	...	1 gramme	...
10	5,360	1 gramme	...
25	3,860	...	0.1 gramme

This patient never returned for further investigation.

Case 4. Male, mixed race, 22; fever without localized symptoms, enlarged groin glands both sides; condition cleared before injections.

Preliminary Count: at 9 P.M. 2,310 in 1 cc.

Day	No. per cc.	"Bayer 205"
1	2,310	1 gramme
2	...	1 gramme
3	...	1 gramme
9	...	1 gramme
10	1,050	...
16	6,120	1 gramme
23	4,840	1 gramme
26	650	...
27	...	1 gramme
29	8,250	1 gramme
33	4,690	1 gramme
35	460	1 gramme
38	2,815	...
40	5,110	...
45	935	...
52	7,120	...
54	3,155	...
55	10,395	...
56	5,600	...
57	3,655	...
58	5,755	...
61	6,035	...
66	4,270	...

Case 9. Black, male, 45; had never had any attacks; received 2 grammes "Bayer 205," but never returned.

Case 10. Male, mixed race, 15; had had no attacks for some months; preliminary counts showed over 1,000 embryos per cc. at 9 P.M.:—

After Treatment

Day	No. per cc.	"Bayer 205"
1	...	1 gramme
2	...	1 gramme
3	...	1 gramme
6	345	...
10	...	1 gramme
13	2,580	...
17	...	1 gramme
19	...	1 gramme
26	655	...
32	735	...

(At this stage, the patient had an attack of acute *lymphangitis* in the right leg with fever and ague, lasting 2 weeks.)

43	355	...
57	215	...
71	195	...
77	90	1 gramme
84	120	1 gramme
91	865	1 gramme
93	625	..
95	560	1 gramme
98	315	...
100	460	...
102	490	...
105	160	...
107	160	...
112	740	...
119	970	...
121	985	...
122	1,160	...
123	1,110	...
124	750	...
125	420	...
126	820	...
128	960	...
149	975	...

It thus appeared that, following the administration of the drug, the number of embryos in the peripheral night-blood showed an initial increase, followed by a decrease, — eventually, however, gradually returning to the previous level, even after the administration of 10 grammes.

To ascertain whether untreated patients showed a similar rise and fall in the number of circulating embryos, the following controls were investigated: —

Case 5. Mixed race, male, 8 — (Control).

Day	No. of embryos per cc.
1	8,500
16	15,590
18	10,520
29	11,605
43	15,995
47	60,000 (*at 10 P.M.*)
52	13,210
71	22,675

Case 6. Black, male, 33 — (Control).

Day	No. of embryos per cc.
1	3,570
13	5,815
16	9,130
20	6,545
24	8,770
32	10,225

The patient, at this stage, went into the interior of the Colony and was thus lost sight of.

Case 7. Black, male, 40 — (Control).
Treated with Antimony Potassium Tartrate.

Day	No. of embryos per cc.	Antimony Pot. Tartrate
1	3,660	0.1 gramme
3	7,275	0.1 gramme
5	3,360	...
6	...	0.2 gramme
9	4,575	0.2 gramme
13	4,070	0.2 gramme
17	2,490	...

Case 7.—Continued.

19	2,465	0.2 gramme
22	2,200	0.2 gramme
24	3,140	0.1 gramme
27	4,300	0.1 gramme
31	3,770	0.1 gramme
34	5,150	...
45	3,565	...
		Total 1.5 grammes

Case 11. Male, European, 35 — (Control).

Day	No. of embryos per cc.
1	415
3	690
10	155
13	1,015
16	605
35	1,370
38	605
40	1,475
52	560

It would appear, from a careful consideration of these results, that, quite apart from treatment or the occurrence of lymphangitic attacks, one finds a periodical waxing and waning of the numbers of embryos circulating in the peripheral blood. At intervals of 1, 2, 3 or 4 weeks, as the case may be, the numbers of embryos seem to reach a maximum, from which point they gradually decline until a fresh accession of embryos occurs.

Where the infection is light, as in cases 10 and 11, this character is either masked or exaggerated — if comparatively small amounts of blood be examined — owing to the fact that the embryos are apparently not uniformly distributed in the peripheral blood.

Where over 2,000 embryos per cc. of blood are present, however, and at least 200 cmm. of blood are taken, this character is clearly brought out.

Nevertheless, in such infections the number never declines in so pronounced a manner in untreated controls as it does

during, and for some time after, the administration of "Bayer 205." Moreover, this fall is preceded by a very marked rise in all cases.

For example, No. 2, after 1 gramme of "Bayer 205," showed a rise from 5,750 to 10,560 per cc., then a gradual decrease to 3,860 in 25 days, after which no further examinations could be made.

No. 4 showed a rise from 2,310 to 6,120, then sank to 650 per cc. in 26 days, to 460 in 35 days, and to 395 in 45 days, in each case increasing in the intervals.

No. 10 was a case of comparatively light infection, but the number of embryos rose to 2,580 and then sank to 655. At one time he showed only 90 per cc.

It appeared, therefore, that "Bayer 205" produced some effect on the numbers of circulating embryos and it seemed necessary to ascertain, if possible, whether this effect was produced directly on the embryos or through some action on the parent worms.

Experiments *in Vitro* with "Bayer 205"

The following dilutions of "Bayer 205" were prepared:—

1 — 250, 1 — 2,500, 1 — 5,000

Two series of these dilutions were made, one series with citrated saline, and the other with normal saline to which about 0.4% Potassium Oxalate was added.

A small quantity of each of these dilutions was added to an equal quantity of heavily infected blood; this combination was thoroughly mixed and hanging-drop preparations were made, so that the final dilutions were 1 — 500, 1 — 1,000, 1 —5,000, and 1 — 10,000. These preparations were immediately sealed with paraffin, stored in the ice-box, and examined at intervals.

Similar control preparations were also made, without the addition of "Bayer 205" or any other drug.

In the citrated blood, the last occasion on which any movement of the embryos could be made out was 43 hours after the preparation had been made.

No movement of the embryos could be made out in the blood mixed with "Bayer 205" after 19½ hours; at this period the embryos were very sluggish, but movement was made out even in the 1 — 500 dilution.

In the oxalated blood, however, the embryos appeared to be as active in the solution of "Bayer 205," even up to 1 — 500, as they were in the controls, and movement was made out in both up to 43 hours after the preparations had been made.

There was, therefore, no evidence that "Bayer 205" exerted any toxic effect on the embryos.

As it was possible, however, that, though without toxic effect *in vitro*, the drug might be toxic *in vivo* by virtue of products formed by inter-action with substances present in the circulating blood — as is stated to be the case with Atoxyl[1,2] — some cutaneous blood was taken at 9 P.M. from 2 heavily infected patients — one untreated, and from the other 24 hours after he had received his 3rd dose of 1 gramme of "Bayer 205," 1 gramme having been administered each day for 3 successive days.

Three portions of blood were taken from each case, one undiluted, one mixed with citrated saline, and the 3rd with saline to which 0.4% Potassium Oxalate had been added. Hanging-drop preparations were made, sealed with paraffin, and stored in the ice-chest.

In the control blood no movement was made out after 61 hours in the citrated, or after 13 hours in the oxalated, specimen.

In the treated blood, no movement was made out after 36 hours in the citrated, or after 31 hours in the oxalated, blood.

Moreover, it has been shown that, after the administration of "Bayer 205," actually more embryos than had before been present could at certain intervals be found in the peripheral night-blood of the same individual taken at the same time. There is, therefore, no evidence that "Bayer 205" exerts any toxic action on the embryos, so that the temporary reduction in this number is probably due to some action on the parent worm.

"Bayer 205" is described by Dr. Kleine[3] as a complex organic body, containing neither Arsenic, Mercury, nor any

[1] Manson-Bahr; "Filariasis and Elephantiasis in Fiji," p. 78.

[2] Manson-Bahr; *loc. cit.*, p. 13.

[3] Kleine; "On a recent expedition to Africa to investigate the action of 'Bayer 205' in Trypanosomiasis": *Transactions of the Royal Society of Tropical Medicine and Hygiene*; Vol. 17, No. 8, Feb. 21, 1921, pp. 445, 463.

other metal, its nucleus being Trypan-blue, the substance originally employed by Professor Nuttall in his experiments.

Anderson[1] has recently published the results of the administration of Oscol Arsenium, Oscol Cuprum, Oscol Hydrargyrum, Oscol Manganese, Oscol Stibium, Sodium and Potassium Antimony Tartrate, Aniline Antimony Tartrate, and Quinine Antimony Tartrate, as judged by repeated counts of the embryos in a measured quantity of the peripheral blood. In all cases he used 20 cmm. of blood.

In no case, if a careful examination of his results be made, is there a result comparable to that which I have shown to follow the administration of "Bayer 205." In one of his cases, treated with Oscol Stibium, the number of embryos gradually fell from 1,900 per cc. to 150 and then disappeared, but this followed an acute attack of *lymphangitis*, while the other 7 cases showed no such result.

It seems clear, therefore, that a filaricidal drug should be sought, not from among compounds of Arsenic, Antimony or other metals, but rather from among the group of substances to which belong such bodies as "Bayer 205."

Recently, however, F. Noc[2] has claimed that the embryos of *F. bancrofti* in the blood are destroyed by intramuscular injections of Amino-arseno-phenol (compound No. 132 of Dr. Pomaret), though this drug appears to have no action on the parent worms.

If this is confirmed, the task of finding a drug which kills the adult worm will be greatly simplified, and I have already asked for a supply for experimental purposes.

Summary of Conclusions

1. In trying to estimate the effects of drugs on the adult *Filaria bancrofti* by counting the embryos circulating in the blood, 20 cmm. of blood is an insufficient amount to use. Comparatively large quantities of blood — at least 200 cmm. should be drawn off.

2. The number of embryos shows periodically an alternate rise and fall, but these excursions are comparatively slight

[1] Anderson and others; "London School of Tropical Medicine, Research Memoir Series," Vol. 5, 1924; Memoir 7, "Filariasis in British Guiana."

[2] F. Noc; *Bull. Soc. Path. Exot.* 1923, Vol. 16, No. 2, Feb. 14; pp. 126 — 132. *Summarized Tropical Diseases Bulletin*, Vol. 20, No. 12.

in untreated individuals, not the subjects of lymphangitic or other inflammatory attacks.

3. "Bayer 205" causes a sharp initial rise, followed by a pronounced fall, which is, however, only temporary, though it may be noted from time to time for 2 or 3 months.

4. No untoward results followed the administration of this drug to out-patients, nor was there any evidence of permanent damage to the kidneys.

5. The effect of the drug seems to be produced through some toxic action on the parent worm, and not on the embryos.

THE ETIOLOGY, SYMPTOMATOLOGY AND TREATMENT OF INTESTINAL AMEBIASIS

W. M. James, M.D.,
W. E. Deeks, M.D.

Introduction

In 1914 the writers published the results of their experience for 6 years in Ancon Hospital, with respect to the diagnosis, symptomatology and treatment of Amebic Dysentery. As will be shown later, exceptional and ample facilities were afforded for the study of all phases of human infection with the entamebas of the intestinal tract. Deeks correlated the data on the clinical aspects and the treatment, while James made a study of the entamebas themselves, with respect to the association of their various types with the symptomatology of the infections.

At this time Deeks demonstrated at least 14 different etiological factors in the Canal Zone, responsible for the symptoms of dysentery. Many of these factors, it is true, were infrequently concerned in our Clinics, but none the less had to be taken into consideration in establishing a diagnosis. In a country where any dysentery may or may not be amebic, it is of the highest consequence correctly to establish the etiology, if serious results for the patients are to be avoided. It is indeed true that the experienced clinician can often accurately establish a diagnosis of acute, sub-acute, or chronic amebic dysentery on symptomatology alone, but should he rely solely on this, he will have frequent occasions for regret.

The necessity of correctly diagnosing amebic dysentery is shown by a comparison with other dysenteries with which it may be confused. Deeks listed the following forms of dysentery which occurred with more or less frequency in his

service in Ancon Hospital as Chief of Medical Clinic for the Canal Zone.

1. Amebic dysentery caused by the *Entameba histolytica* of Schaudinn.

2. Bacillary dysentery caused by Shiga's or Flexner's bacillus, and the allied varieties.

3. Bilharzia dysentery caused by the *Schistosoma mansoni.*

4. Balantidium dysentery caused by the *Balantidium coli.*

5. Malarial dysentery in the course of a general malarial infection.

6. Tubercular dysentery due to tubercular ulceration of the intestine.

7. Nephritic dysentery, or dysentery associated with acute diffuse nephritis, or secondary to a chronic nephritis with an acute process superadded.

8. Diphtheric dysentery or colitis, associated with a diphtheric or gangrenous inflammation of the mucous membrane, of the whole colon, rectum, and part of the adjacent small intestine, — a very fatal form.

9. Dysentery in the course of pellagra.

10. Dysentery resulting from the ingestion of decomposing meats or fish.

11. Dysentery resulting from the ingestion of infected milk. These (10 and 11) may be bacillary in character.

12. Dysentery secondary to cardiac or hepatic disease.

13. Dysentery associated with typhoid ulceration of the bowel.

14. Clinical dysentery, which comprises the greatest number of cases and embraces that large group, of undetermined etiology, which occur here usually about May, in large numbers — about the close of the dry, and the beginning of the rainy, season. No microscopical or cultural findings have enabled us to determine the etiological factors. It is not very severe, lasting usually from 4 to 10 days, and requiring no specific treatment. If, however, any of these dysenteries be associated with *Entameba coli*, to the uninitiated they are grouped as amebic dysentery, and hence give rise to mistaken statistics.

The type referred to under No. 14, as occurring at the beginning of the rainy season, and the various bacillary types,

will be fully discussed by Bates and Connor. At this time they are much more frequent in the Canal Zone and the cities of Panama and Colon, than is the amebic type. The importance of these, and of the other types, is that they may, and do, occur in the presence of infections due to *E. histolytica* and *E. coli*, and the etiological factors must be determined if successful treatment is to be had. As noted by Deeks, dysentery is but a symptom, and not in itself a pathological entity.

During the course of our studies we were impressed with the relative frequency of the latency of infections with the pathogenetic entamebas, with respect to dysenteric symptoms, either past or present. Dr. A. B. Herrick, at that time Chief of Surgical Clinic in Ancon Hospital, found that over 20% of his cases of hepatic abscess gave no history of dysentery. Deeks noted the symptomatology in cases of pathogenetic amebic infection without dysentery, while James ascertained that entamebas which then were variously termed *E. tetragena* and *E. minuta* were encountered in stools of patients who had no dysentery at the time of observation, nor any previous history of it.

The result of our studies was to convince us that there were, in the territory from which our patients came, but 2 species of entamebae infecting the human intestinal tract. One only of these, *E. histolytica*, was pathogenetic, while the other, *E. coli*, was a harmless commensal. We were of the opinion that *E. histolytica* took on a great variety of forms, according to the particular phases of environment in its life cycle, and all these forms belonged to a single species. We published these conclusions, as noted, in 1914. With respect to our opinion as to the life cycle of *E. histolytica*, we were antedated by E. L. Walker, who arrived at the same conclusions, in Manila, in 1911, but whose work did not reach us until after our own had been completed. Dobell gives to James credit for first noting the formation of the very small cysts in histolytica infections; but, as we stated at the time, Walker was unquestionably the first to assert the identity of species for the varying aspects of *E. histolytica*.

In 1914 we were of the opinion that most *E. histolytica* infections are associated at one time or another with acute, sub-acute or chronic dysentery. For reasons that will

presently follow, we have revised this statement. At that time we were concerned mostly with dysentery. We labored especially on the differentiation of amebic from other forms of dysentery, as did most other workers; recognized that diarrhoeas without dysentery were frequently associated with *E. histolytica* infections; and knew that in some cases the evidence tended to show a true latency of this species with respect to symptomatology.

Although routine stool examinations were made on all medical cases, most of the ward physicians who made these examinations, while recognizing readily the large vegetative types of both *E. histolytica* and *E. coli*, did not have the special training necessary to distinguish the small vegetative, pre-cystic and cyst-forming generations, especially those of *E. histolytica*. Stools passed early in the night frequently were not examined routinely until late in the morning. We have no doubt that under these circumstances a very considerable proportion of amebiasis was overlooked. We are sure it will be agreed that long training and much personal experience are needed successfully to identify the small precystic and cyst-forming generations, and wet fixation and staining must be used at times in doubtful instances.

Since 1914 one of us has had opportunity to study a widespread distribution of amebic dysentery in the hospitals of the United Fruit Company. The other has had experience with intestinal amebiasis in all its forms, in the Herrick Clinic and the Hospital de Panama, as a result of personal study of symptoms and stools of several thousand patients, surgical as well as medical, and owing to the coöperation and aid of Dr. A. B. Herrick and Dr. R. W. Runyan, with whom he is associated, in the many cases of amebiasis with surgical complications. In this paper we have correlated the results of more than sixteen years of continuous work on Intestinal Amebiasis, and present for consideration these propositions, in whose support we shall presently bring forward our evidence.

1. Intestinal Amebiasis is a widely spread and very common tropical infection, especially that type due to *E. histolytica*, and is extremely varied in its symptomatology. It may remain latent, without symptoms, and acute, sub-

acute, and chronic dysentery are not its most frequent manifestations. These latter are more frequently referable to gastro-intestinal disturbances without dysentery.

2. *E. histolytica* is the important etiological factor in producing the symptomatology of this infection, and often is aided by conditions such as stasis which bring about a temporary or chronic inflammation of the mucosa of the large intestine.

3. The normal habitat of this parasite is the lumen of the large intestine, especially the first part, and it takes on pathogenecity only when it invades the tissues, which is by no means a constant happening. This invasion may be localized or general, and the symptomatology will vary accordingly.

4. There is a very considerable natural resistance of the body tissues, and especially of those of the large intestine, to such invasion, — otherwise all untreated pathogenic amebic infections would terminate fatally.

5. Re-infection from the lumen of the bowel is a very important factor in acute and chronic cases. The improvement that often follows any kind of complete colonic irrigation, whether from above or below, is due to the partial removal and death of the parasites in the lumen, which are very susceptible to any change in environment.

6. Successful treatment should have two objects in view: the destruction of the parasites in the lumen, and that of those in the tissues as well.

In his excellent monograph on Amebic Dysentery, published in 1910, the late Dr. W. Carnegie Brown objected to the use of the word "amebiasis" as a designation of "amebic disease generally," on the grounds that "while symptoms other than dysentery have been produced by amebic infection . . . such an event is unusual." He distinguished hepatic and cerebral abscesses, "and other consequences of infection" without precedent dysentery and, like others who wrote at that period, recognized that the development of amebic dysentery is often insidious.

But to Dr. Brown, and many more of us at that time, the infecting agent, *Entameba histolytica*, was known only in the relatively large vegetative stage, and the small precystic and cyst-forming generations had not been recognized.

Even today the literature of amebic infection is concerned mostly on the clinical side with the treatment of the dysenteric stage, and efforts to eradicate the infection entirely; though a review of the past 10 years shows a growing recognition and appreciation of the effects of infection with *E. histolytica* in cases without precedent dysentery or diarrhoea to any marked degree, and frequently not at all. Many of these effects result in surgical complications such as will follow any inflammation of the large bowel, but many are also amenable to proper medical treatment.

Our own experience has been that acute and chronic dysenteries were much more frequent 15 years ago than today, and we believe that the use of emetin and its modifications has very considerably altered the clinical aspect of amebic infection in countries where these drugs are used in every class of diarrhoea and dysentery with the frequency with which quinine is given in any kind of fever. How much gastro-intestinal disturbance without frank dysentery or diarrhoea, due to amebic infection, occurred before trained workers could find the small types of the entameba, cannot be said with any degree of certainty. But it must have amounted to a very considerable proportion of the total, since today we see more cases of untreated amebiasis without histories of frank dysentery, than we do of relapses following treatment for acute symptoms.

Gastro-intestinal disturbances are very common in the Tropics, and amebic infection, directly or reflexly, can imitate closely most of them. Aside from other factors, over-indulgence in alcohol and unbalanced diets, especially excess of sweets and carbo-hydrates, combined with sedentary habits and lack of exercise, are a fruitful source of chronic illness in this part of the world. It follows from this that much amebic infection, whether or not resulting in dysentery, will be superimposed upon pre-existing gastro-intestinal trouble of all kinds, rendering the diagnosis difficult at best, and indeed impossible without an accurate knowledge of the species of the human entamebas in all their phases.

It will be obvious that the symptomatology of amebic infection is complex, and within the limits of this paper we cannot discuss it in detail. We shall not touch upon that of acute, sub-acute, and chronic amebic dysentery — these

have been ably presented by many writers — but shall confine ourselves to the less commonly reported aspects of intestinal amebiasis. Here we should note that since making ourselves familiar with the small pre-cystic and cyst-forming generations, with one exception we have never failed to find *E. histolytica* in the stools in cases of liver abscess, and other surgical complications shown at operation to be due to amebic infection. We are often led to predict such complications, and in other cases to avoid operation, by use of this knowledge, as will be seen.

Etiology

The etiology, symptomatology, pathology, and some of the complications of Amebic Dysentery have been thoroughly described in the literature of the past 20 years. Most of this, however, refers to the acute and chronic forms of amebic dysentery and abscess of the liver. It is essentially a literature of acute and chronic infection, with entamebas of the pathogenetic type. It has been noted by several writers, particularly by Dr. C. B. Wenyon, that *E. histolytica* infection without dysentery is relatively common in endemic foci; and it is common knowledge that between the intervals of dysenteric attacks many patients enjoy relatively good health. However, Intestinal Amebiasis — that is, all of the phases of an infection of the large intestine with *Entameba histolytica* — has not been considered to any great extent by workers in Tropical Medicine.

Text books on pathology describe the lesions associated with the various forms of amebic dysentery, and also with amebic abscess of the liver; but they do not take up the many other complications, some of them very serious, which are found in all degrees of Intestinal Amebiasis. Even amebic abscess of the brain is not mentioned by MacCallum (1920) nor by Stengel and Fox (1921). These lesions will be referred to by Dr. R. W. Runyan, and Dr. H. C. Clark, in discussion of the surgical complications and the pathology of Intestinal Amebiasis. Some of them, as far as we know, have not been described before and, we believe, will be found of interest.

Intestinal amebiasis is protean in its symptomatology, and acute and sub-acute dysentery are not its most common

manifestations in the large endemic focus consisting of Central America, Peru, Ecuador, Colombia and Venezuela. (These countries are included because of personal knowledge. The focus is much larger.) There may be a relative immunity, among natives of these countries, to the dysenteric phase of the disease, because this does not appear as the most constant form among them, but there is, in our opinion, another reason, which we shall discuss under "Symptomatology." It is probably the most wide-spread protozoal infection in man, including even malaria, in the part of the world just referred to, with perhaps the exception of infection with some of the intestinal flagellates.

We shall give here the results of our personal experience and observation, rather than attempt a comparison of these with those of other writers. It is impossible to attempt such a comparison except in an extensive monograph. Our views on the species of the entamebas of man were set forth in the "Annals of Tropical Medicine and Parasitology," in July, 1914, and what we have seen since has only served to convince us that there are but two such species. We are aware that there are reasons for a difference of opinion on this point of view, and we are sure that these will be brought out in the discussion.

In the early days of the construction of the Panama Canal, amebic infection was relatively common. There was a very large West Indian population; and between 1906 and 1912, some 5 or 6 thousand Southern Europeans, mostly Spaniards, but with a considerable proportion of Greeks and Italians, and other races of the Mediterranean littoral, were also here. Among these people there was enough amebic infection to make possible a study of this condition in all its phases. At first we did not distinguish between *Entameba coli* and *Entameba histolytica* and, in fact, it was not until 1908 and 1909 that we began to recognize the small entamebas of the *histolytica* type in the generations that precede cyst-formations, and also cysts themselves.

Among the large American population, amebic infection was not common. Most of the cases occurred among the West Indians and the Europeans. Today amebic infection originating in the Canal Zone, and in the cities of Panama and Colon, is uncommon indeed, and in most cases that come

from these localities there is a reasonable supposition of infection elsewhere.

But in the interior of Panama, and in the countries above referred to, Intestinal Amebiasis is very widespread. Our personal experience in recent years has led us to believe that it is common in cities and towns, as well as in the country districts; and climatic conditions in the Tropics, as determined by altitude, have very little influence upon its distribution.

To the hospitals in Panama and the Canal Zone come a great many patients from the surrounding countries of Central and South America, and among these every year are seen some 75 to 150 cases of amebic infection. Most of them do not come with dysentery. During the World War one of us was detailed to the Southern training camps, where he saw quite a few very interesting cases of amebic infection, to which reference will be made later. We mention this to show that the entamebas which we have seen, come from widely separated localities, and an opportunity has been given to observe whether a difference in locality is responsible for any difference in species or in morphology.

We may state here that we have observed no such difference, and in our opinion *Entameba histolytica* and *Entameba coli* are the same in South Carolina as in Peru, and in California as in Venezuela. It is impossible for us to obtain accurate statistical data, as most of our patients are sojourners, and in hospital temporarily for treatment. But in the course of the last 15 years we have seen and treated enough local cases, and others which we could follow later, to gather some evidence which we trust is not without value.

We shall not go into a description of the entamebas themselves; for in our opinion the identification of them, and the method of distinguishing between the harmless *E. coli* and the pathogenetic *E. histolytica*, can be gained only by considerable personal experience and familiarity with microscopic and staining technique. In this respect we are thoroughly in accord with Wenyon, whose very able work is entitled to the highest consideration. Entamebas associated with the various forms of dysentery are readily found and classified. But the entamebas of the end stages of the cycle are often very difficult to see. The vegetative forms

of the entamebas associated with the dysenteries retain their vitality for a considerable period, and the more acute the infection the greater the virility of the vegetative form. But the very small vegetative forms lose their motility quickly, and when motionless are indeed difficult to distinguish from other intestinal cells and inhabitants. It is rather our purpose to place before you other factors in Intestinal Amebiasis.

Certain set phrases, forms, and conceptions, which are entirely inaccurate, have crept into the literature, and are to be found even in authoritative text books. To one of these in particular we shall call your attention. One frequently reads that a cure has been brought about, as the active entamebas have disappeared, and only cysts remain. As we shall presently explain, as long as cysts are present in the stools, there is an active amebic infection higher in the large bowel, and it is erroneous to believe that, because only cysts are found in the stools, they represent the sole type of entamebas present in the colon.

METHOD OF INFECTION

Amebic infection in man is primarily located in the large intestine. We believe that the only method of infection is through the oral ingestion of cysts, contained mostly in moist particles of fairly fresh fecal matter. The active entameba, in the vegetative and pre-cystic states, is a very delicate and perishable organism, and requires a liquid or semi-liquid surrounding medium in order to exist. It is killed immediately on the slightest exposure to air, to certain acid media, or to any one of many substances in weak dilutions. If a few drops of ordinary tap water, or even distilled water, are added to a preparation containing active entamebas, and well mixed with this, these are promptly killed and at once begin to disintegrate. Unless there is some unknown vegetative form that can exist outside of the human body, the cyst is the only known method of transmission.

Amebic ulceration does not occur in the stomach, nor in most of the small intestines, and all authorities agree that except in advanced infection, it is rare to find ulceration even at the lower end of the ileum. The cecum, however, and the appendix are frequently infected. MacCallum states that the appendix is not involved, but we have had

several cases in which the pathologist returned a report of sub-acute inflammation due to the presence of entamebas in the tissues of the appendix. The parenchyma of the liver is very susceptible to the destructive action of the entamebas, as is also that of the brain. Muscular tissue is less susceptible, and it is fortunate that this is true, — otherwise the mortality in amebic infection with colonic ulceration would be as high as that in any other infectious disease.

Dr. Runyan and Dr. Clark will give you a description of 2 very interesting cases in which there was a widespread destruction of the tissues of the chest wall. We have never seen a general involvement of the tissues of the body, and an accurate explanation of why this does not occur in some cases would be very interesting and profitable.

All of this proves a highly selective habitation for the active vegetative forms of the pathogenetic entamebas, and the same is true of the non-pathogenetic *E. coli*. Further evidence is supplied by the fact that neither *E. coli* nor *E. histolytica* has been successfully cultivated, and claims to this effect have not been substantiated to the satisfaction of those familiar with the morphology of these parasites. We should like to refer here to the excellent work of E. L. Walker on this subject. His experiments were exhaustive, and while he frequently cultivated the so-called free living amebas, at no time did he cultivate entamebas resembling the entamebas of man. This has also been our experience in the Canal Zone. Dr. S. T. Darling made some very careful experiments, with the same result.

The cysts themselves are also perishable, and do not withstand exposure to drying or to change of liquid mediums for any length of time. If a small piece of feces, heavily infected with cysts, is put on a glass slide, and its external surface allowed to dry, and then a smear is made, it will be seen that the cysts in the dry parts disintegrate very rapidly, while those in the moist, central part keep their normal appearance. If particles of feces containing numerous cysts are kept in a moist chamber at body heat, or even lower, within 2 or 3 days the cysts will disappear.

In the latter case, if examinations are made serially it will be found that small entamebas develop within the cysts, and often can be demonstrated free in suitable preparations.

This may explain the apparent success of certain cultural experiments. Further, the cysts themselves will not live for any appreciable time when thoroughly mixed with water. If small proportions of heavily infected feces are thoroughly mixed with milk or with water, and allowed to stand overnight, the mixture when fed to young kittens often will not infect them, although these animals are quite susceptible to artificial infection with fresh material containing large numbers of cysts. However, in their own proper environment cysts will maintain their normal shapes and staining reactions for several weeks. We have kept cysts sealed between cover glass and slide until the interior has begun to dry — a period of perhaps 6 weeks. But changes of environment seem to have a harmful influence upon them. Under circumstances in which infected humans are crowded together in very unsanitary and unclean conditions, especially in wet and damp places, a very favourable environment would be procured for prolonged exposure to infection. This was particularly noted by the French writer, Dr. Jacques Carles, as a cause of small local epidemics among troops in the advanced trenches. If it were possible for cysts to remain viable in a given water supply, an enormous amount of these would be necessary to bring about even a small proportion of infection among those using it.

These reasons impel us to the opinion that amebic infection in man is for the most part conveyed by the swallowing of particles of fairly fresh fecal material, perhaps in minute quantities, but containing large numbers of cysts in their moist centers, though external surfaces may be dry. We know that Ascaris infection is conveyed in a similar manner, and Ascaris infection is as common among adults and children as is amebic infection in the part of the world to which we have reference, and the two are very frequently associated. Flagellate infection is probably conveyed in the same way. It seems to us improbable that a water supply, even though heavily contaminated with human fecal material, is responsible for the conveyance of much of the prevalent amebic infection in man. Dr. H. C. Clark is not in entire agreement with this statement, but we believe that later the difference of opinion will prove to be more apparent than real.

We believe that dysentery in epidemic form, following flooding of wells, contamination of water supplies, and changes of season, is due to the bacillary type of infection; and when such epidemics take place in endemic foci where there is a great amount of Intestinal Amebiasis, mixed infections should occur in a considerable percentage of cases, unless the altered conditions produced in the bowel prove unfavorable to the entamebas themselves. It is true that there is a correlation in statistics between areas in which amebic infection is predominant and a polluted water supply is also present. But it is also true that places which tolerate polluted water supplies, have a considerable population which is very filthy in its personal habits; and these habits change with improved sanitation and sewage and more easy access to methods of cleanliness. The pernicious practice of using human feces as a garden fertilizer is undoubtedly responsible for much endemic infection, and there is a notorious association in tropical countries between amebic dysentery and the eating of fresh vegetables. Amebic dysentery also relapses frequently after any indiscretion in diet which leads to a colitis, and it may very well be that a polluted water-supply will assist in the development of cases of amebic dysentery that might otherwise remain latent.

One has but to see the water closets, toilets, privies or even simple outdoor depositories in many places of this part of the world, in the large cities as well as in country districts, to be convinced that the chance of getting hold of small bits of infected feces in one's food are very good. The lower class of people is exceptionally filthy. A cook or a waiter who is careless in the matter of cleanliness can easily convey minute particles of infected material to food which is being prepared or served. Flies undoubtedly aid in the transmission of infected material. This was shown by Wenyon and O'Connor in their carefully thought out experimental work. Some years ago several cases of amebic dysentery were discovered among the children of a prominent local family and attributed to the supply of drinking water. Investigation showed that the nurse who prepared the food for these children was heavily infected, and had had a diarrhoea alternating with constipation for a long time.

The classical experiments of Walker and Sellards in the Bilibid prison in Manila, in 1913, showed that fecal material fed to humans did not infect when vegetative entamebas only were given by mouth, but that infection followed in a certain percentage of cases when material containing even a small number of cysts was given.

As we have stated, the human entameba is a very highly selective organism. Even in such animals as dogs and cats, in which artificial infection may be brought about, and which have abundant access to food containing heavily infected human feces, *E. histolytica* and *E. coli* are not found, although other species have been reported. Indeed, there are many species of entameba found in the intestinal canals of organisms ranging in the scale of life from the higher ape to the lowly cockroach, but none of these corresponds to the peculiarities of the entamebas of the human intestinal tract. Just as the malaria parasites, in their vegetative and sexual form, arise only in human beings, although similar protozoa are found in birds and animals, so *E. coli* and *E. histolytica*, except under artificial conditions, exist only in man; the difference being that malaria requires an intermediate host for its transmittal, and no such host has been demonstrated for the entameba.

THE LIFE CYCLE OF THE HUMAN ENTAMEBAS

Much of the confusion with respect to the various species of human entamebas has been due to failure to regard the life cycle of these as a whole, and to insistence upon certain morphological phases of this life cycle as characteristic of species. After all, the entameba is a very simple type of life, though adapted to a peculiar environment. It is a peculiar unicellular organism, made up of a nucleus, and a cytoplasm; divided into an internal part, or endoplasm, and an externl part, or aectoplasm; and endowed with an unknown potential of virility. Seen under the microscope, it appears flat, owing to the confined space between the cover slip and slide, but viewed in a hollow chamber, it is globular in form. It is difficult to see under this latter condition, owing to the thickness of the preparation. Fixed and stained smears show its nucleus to be made up of the same materials as the nuclei of other simple uninuclear cells; and its cyto-

plasm is also similar to the cytoplasm of other simple cells. Any one who has seen the entamebas, either in fresh or in fixed and stained preparations from cases of acute dysentery, when numerous cells from the mucosa of the intestine are mixed with them in the preparations, will recognize this similarity.

Yet, on account of almost infinitesimal arrangements of chromatin on the nuclear membrane, and various aspects of the stained or fresh cytoplasm and nucleus, many observers have attempted to differentiate species, — and some of these have been famous protozoölogists, such as Schaudinn, who have not taken into consideration the numerous changes which take place in the living and stained organisms in various phases of the life cycle. The result has been to classify various stages of life of the same organism as different species. *E. coli* is much truer to type, and shows much less variation than *E. histolytica.* This is due to the far more active life of the latter, but in both species the main events of the life cycle are very similar. We do not speak of the life cycle of an individual entameba, but rather of the life cycle of numerous individuals taken collectively, — as one would survey the various aspects of birth, growth and death of the inhabitants of a certain city of homogeneous population over a period of many years.

How long an individual entameba lives in any one particular form is not known, but in the cultivated species of amebas the individual, as such, divides rapidly, and the colony waxes or wanes as a whole. The cycle of the entamebas in the feces is quite different from that of those who make their way into the tissues. These latter seem to maintain a uniform potential of vitality which results in a succession of homogeneous generations, due perhaps to a constancy in the surrounding medium and in the food supply, — while those in the intestinal tract change rapidly in altered conditions, and exhibit many generations of the same species in a relatively short space of time. Degenerating forms are found in tissue preparations, but not the pre-cystic or cyst-forming generations, nor cysts themselves. In time, in many instances the tissue invading organisms die, probably because their virility or their proper food supply becomes exhausted; or else we would not have undoubted cures brought about by

administration of drugs that could not possibly affect the organisms in the tissues themselves.

The changes of the cycle can be shown by selecting an ordinarily acute amebic infection. If there is acute dysentery, for the most part, a large very actively motile type will predominate. If the patient is put to bed, and an easily-borne diet which contains a certain amount of "roughage" is given, within a day or two the character of the stools may alter, and they may become firmer. The type of entameba in the feces immediately changes, a smaller generation is seen, and with it many degenerating entamebas. If the stools remain soft for a day or two the entamebas decrease in size, and eventually a generation will be found in which the individuals are not much larger than leucocytes, and precystic and cystic forms will begin to appear. If the stools continue soft for a week or so, very often encystment to any extent does not take place, and the entamebas persist, sometimes in large numbers as very small vegetative organisms which are quite difficult to distinguish. This particular type as noted above, loses its motility very rapidly.

These vegetative organisms correspond in their cytoplasm to those described by various writers as *E. nana*, but seem to be smaller than those of the type of this organism which have been described. However, in all of our stained specimens these organisms constantly show a reticulate nucleus, and not the heavily stained, partially globular nucleus of the single karyosome type described for *E. nana*. This change, however, is not due to a diminution in vitality on the part of the entamebas considered as a whole, but is an adaptation of a portion of the species to conform to its external surroundings, and to a diminished food supply; and also to carry on life and vitality under unfavourable circumstances.

If a purge is given at this time and the watery stools are examined, and especially the flecks of mucus that are brought away in these, the same large active entamebas will be found as were present in the dysenteric stools. It is a wonderful process of adaptation to environment and necessity, that within the space of a few feet in the large intestine a simple unicellular organism will so quickly alter and change.

During this process there are marked nuclear and cytoplasmic changes. As long as active dysentery prevails, the entamebas are of the large actively motile type. When the stools begin to harden, entamebas of a smaller and more sluggish type may be the only ones found for days and weeks, and the numerous variations in type among these generations are responsible for the many different species which have been classified from time to time.

But the mother type, that is, the large actively motile entameba, shows very little variation in the active and virile forms, — only in those that are degenerating and dying or that are going on to cyst formation is there any particular variation. Not all of the large forms multiply and so continue their lives indefinitely; in many individuals, although not in the group in general, the potential of vitality becomes exhausted, and this results in numerous and very curious alterations in the structure of the nucleus and of the cytoplasm; here again the microscopists determine species on morphology only.

The life cycle of *E. histolytica* has been worked up by us from a combination of examining the stools, and securing specimens from high up in the large intestine or from liver abscesses, as a result of complications demanding surgical intervention. Not all persons with amebic infection have dysentery. In fact, we have come to regard typical amebic dysentery as of rather infrequent occurrence in the large number of amebic infections which we have seen in the past 15 years, for reasons given later.

In many cases in which there has been no history of dysentery, or, at the most, occasional bloody or mucous stools for very brief periods, the entamebas found in the stools are of the pre-cystic and cyst-forming generations which were so ably and accurately described by Dr. Elmassian many years ago as *Entameba minuta.* From time to time we have had the opportunity to examine appendices and other tissues taken from such cases. In quite a large proportion *E. histolytica* of the *tetragena* type was found. These were very true to type, and, as frequently no inflammatory reaction in the appendices due to the entamebas themselves could be demonstrated by the pathologist, it is logical to suppose that this type represents the ordinary vegetative stage in which the

potential of vitality is sufficient to keep the life cycle uninterrupted.

In these countries amebic infection is very common, and so are sub-acute and chronic appendicitis, so that the finding of the two together by no means establishes an etiological relation between the amebas and the appendicitis. We have come to regard this type of *Entameba histolytica* (the *tetragena*) as more or less latent at times, because examination of the intestine by the surgeon frequently reveals a normal condition; although not rarely instances of infiltration of the submucosa of the appendix by entamebas, with or without adhesions, with an inflammatory reaction have been reported, and have also been found by us.

Perhaps such an infection, for reasons of lack of proper environment or stimulation, has not set up enough activity to produce the pathological findings of amebic dysentery. Not all of the persons artificially infected by Walker and Sellards showed acute dysentery. It may be that a lowered resistance from any cause allows the entamebas to bring about in the large intestine pathological changes which result in dysentery. In chronic cases, dietary indiscretions frequently precede a relapse. However, when dysentery sets in, the entamebas increase in size and in activity as the cycle takes on added virility. The nuclear changes show that a very active growth process by binary division is taking place. This may be called an adolescent stage of the cycle which brings about the dysentery. It is at this stage that the large actively motile entamebas of the *histolytica* type are found in the stool; this type is usually the only one present.

But it must be remembered that this type can live only in a very fluid medium, and indeed the entamebas which come from the walls of an abscess of the liver or are seen in sections of the intestines are seldom as active or as large in size as those found in the blood, pus, and mucous content of the dysenteric stool. The enormous number of the organisms frequently encountered is strong evidence that an active reproductive process is taking place in the lumen of the intestine. In sections from the intestines, even in the most acute and fulminating types of the disease, the entamebas are sometimes not as numerous as are found in preparations of the stools in severe cases of dysentery. In untreated

cases this very active part of the life cycle does not continue indefinitely. The patient either dies, or a temporary improvement sets in.

In fact, chronic amebic dysentery is notorious for its periods of exarcerbation and intermittency. Moreover, it is a law of Nature that generations of protozoa do provide some method for propagation other than that of simple division in the vegetative form. To accomplish this there is a diminution in the activity of the vegetative generation. We do not know whether this is brought about in human infections, by an immunity of the body, or by a diminution of the virility of the strain of infecting parasites, but we are inclined towards the latter point of view. Just as untreated malarial cases temporarily recover, so do cases of acute amebic dysentery, and the reason in either case why the parasites diminish in number and vitality is not yet clear, although immunity may play a rôle, and it is probably the same in both diseases.

We have discussed at some length these points in the life cycle of *E. histolytica*, for the purpose of demonstrating to you that this organism should be studied in its entirety, if an adequate conception of its morphology is to be had for the purpose of diagnosis. *E. coli* goes through similar changes. In liquid stools it is a large, sluggishly motile parasite, in general, although individuals are quite active. It alters its form in the same manner in response to environment as does *E. histolytica*, and very many departures from type are seen at this time, which enthusiastic observers have classified as new species. Some years ago it was quite generally accepted that there were but two species of the human entameba, but war seems to have been declared again, and recently well-qualified observers have been finding new species. When one considers the many variations which occur in either species, one cannot help thinking that the burden of proof lies with those who do not demonstrate the life cycle in its entirety, but remain content with classification based on morphology of individual specimens found only in the stools.

These two factors in amebic infection which we have discussed — the manner of infection, and the life cycle of the parasite — are but two in an exceedingly intricate problem.

There are many other factors of equal interest; and although the clinical features, and the pathological findings in amebic dysentery have been thoroughly worked out, we believe it will be a long time before all of those concerned in intestinal amebiasis are successfully determined.

THE SYMPTOMATOLOGY OF INTESTINAL AMEBIASIS

The symptomatology of intestinal amebiasis, apart from its complications, varies for the most part directly according to the site and the extent of the intestinal invasion. Local invasions may give rise to great severity of symptoms, without involvement of the rest of the large bowel; but there is no reason to believe that there are minor degrees of infection of the entire colon. When all of the colon is involved, we are in the presence of a grave illness, great prostration, and extreme dysenteric symptoms, with every probability of ensuing portentous complications.

As we have noted, it is not our intention to discuss the symptomatology of acute, sub-acute and chronic amebic dysentery. We will note, with respect to these, only one of the signs which determine in part the gravity of the infection. As this sign may occur in severe amebic infections without dysentery, it is of considerable value in judging the extent of tissue invasion. It occurs also in other abdominal conditions in which bodily resistance is greatly lowered. It was described by Deeks in 1914, as follows:

> There is one other symptom almost invariably present in amoebic dysentery which is of considerable diagnostic and prognostic importance, and that is the doughy, inelastic skin. When a fold is caught up and released, it crawls more or less slowly back into position. We have termed it here *myxenoid*. It is not symptomatic of amoebic ulceration alone, but is present in every ulcerated, necrotic, or chronic inflammatory condition of any of the abdominal viscera, in greater or lesser degree. Its disappearance corresponds with the convalescence of the patient, and it is one of the best indications of his satisfactory progress.

The pathology of intestinal amebiasis is fully dealt with in the paper presented by Dr. H. C. Clark. So varied are the symptoms to which these lesions give rise, directly or reflexly, that a classification would include all gastro-intestinal symptomatology. It may fairly be said that if there is

reason, in any form of disease, to expect prior exposure to amebic infection, this should be excluded or included before arriving at a final opinion. An undetermined fever may be due to a small abscess of the liver, not to be demonstrated by physical examination. Obscure cerebral symptoms may be present with an amebic abscess of the brain, and if the Wassermann test is at the same time positive, the diagnosis is indeed difficult. We have seen such a case.

An amebic abscess of the lung, especially when secondary to liver abscess, may simulate lobar pneumonia so closely that if an error in diagnosis is made, failure properly to evacuate the liver abscess will cost a life. Amebic typhlitis will counterfeit chronic appendicitis so nearly that the diagnosis can be made only by the surgeon at operation. If here, the amebic infection does not involve the appendix, and the cause of the typhlitis is not recognized, the reflex and local symptoms will persist. Peritonitis very rarely occurs except in advanced cases, but may follow a severe local inflammation with perforation, and without dysentery. Invasion of the cecum and the ascending colon, producing a very tender tumor may be mistaken for a pyelonephritis. The same process can proceed to stricture of the gut, with obstruction and malnutrition clinically not to be distinguished from malignancy.

If lesions so severe as these can and do occur in the absence of present or antecedent dysentery, the impossibility of determining the etiology of the minor degrees of infection without proper knowledge of the forms of the infecting parasites as they appear in the stools, will readily be acknowledged.

We have endeavored here to present, not a classification of the symptoms of intestinal amebiasis, since this is all but impossible, but a brief description of the more common forms, excluding dysentery.

1. *Latent Infections.* — These are found most frequently in children; when examining the stools for possible helminth infection, Ascaris and Uncinaria ova are very often met with, and the symptoms are referable to these infections. Frequently the children are entirely healthy. James has seen several cases in which the children were anemic and underweight, but without other illness, and in whom heavy infec-

tions of *E. histolytica* were found. Treatment of these cases resulted in marked improvement, but this may well be attributed to the correct diet followed subsequently.

Not infrequently infections of varying intensity are picked up in adults, in routine examinations, when there have been no definite gastro-intestinal symptoms. But to find an alien or a native who has lived any length of time in the Tropics, and who at some period has not suffered with gastro-intestinal disturbance, is rare in comparison with the total number of inhabitants. Especially among the natives, the diet is very faulty. Some of our patients with liver abscess have been positive in their statements as to lack of previous diarrhoea or dysentery, but are vague at times as to gastro-intestinal distress. Unless there has been a prior tissue invasion in the colon, we cannot understand how the entamebas reached the liver.

The percentage of true latency cannot be determined statistically without repeated and prolonged examination of the stools of all the inhabitants of a given area, — an impracticable task. It would not be correct to make an estimate on a few examinations over a short period. The latent cases would have to be followed for years, to determine if symptoms referable to amebic infection developed later. We can, however, state that within certain limitations true latency does occur.

2. *Digestive Disturbances.* — To cite a single instance in the symptomatology of disease, let us give very brief consideration to the reflex digestive disturbances consequent upon chronic appendicitis. There is no reason to believe that the appendix is the only location in the gastro-intestinal tract, chronic inflammation of which will produce local and reflex symptoms.

Amebic infiltration of the cecum, or of any part of the colon, will produce reflex as well as local disturbance. A very great variety of symptoms are encountered in these cases, and they do not yield, as often the uncomplicated cases do, to simple dietetic or medical treatment.

In such cases the diagnosis can be made only by finding the entamebas, and these are very frequently of the type the most difficult to recognize. Careful palpation of the entire colon will often show a definite and fixed point of ten-

derness — sometimes two or three such points. The radiograph, to which reference will be made later, will show not infrequently a constant filling defect in the wall of the colon, corresponding to the tender point.

Persons with this form of amebic infection are often well nourished, but complain continually of their symptoms. The usual methods of examination reveal nothing in particular, and they are likely to be classed as neuresthenics, as indeed some of them are, and others become later. Repeated stool examinations should be made, and very gratifying results to all concerned will follow proper treatment. The frequent dietary indiscretions, especially overindulgence in sweets and carbohydrates must be corrected as well.

3. *Colicky Pains.* — These are very frequent, and occur with and without constipation, oftenest in cases with alternating constipation and diarrhoea. The patients not rarely give histories of more or less previous severe dysentery, sometimes of several attacks, which have been treated with emetin. Without such treatment we have no doubt but that many of them would have developed chronic amebic dysentery and its complications. Very few of them have dysentery at the time we see them. However, a considerable minority deny positively any antecedent dysentery, and some of these also deny antecedent diarrhoea. The colics for the most part are referred to a definite abdominal location, which may be anywhere along the colon, between the cecum and the sigmoid. They are sometimes very severe. They are likely to be confused with appendicitis, cholelithiasis, renal colic and inflamed diverticuli, but only when complicated by perforation with peritonitis do they present the clinical picture generally known as "the surgical abdomen." In uncomplicated cases the abdomen is soft, and palpation will show a spot or spots of definite tenderness.

The radiograph is of great service in diagnosis, and seldom fails to show definite and fixed filling defects. The correct diagnosis depends, as above, on finding the entamebas in the stools. A saline purge will often bring down mucus from the ulcers, in which large, actively motile parasites are found. Such cases make up the largest proportion of intestinal amebiasis met with in the Herrick Clinic.

4. *Colitis.* — This presents a severer symptomatology than that above described. True dysentery, as differentiated by tenesmus, painful and burning passage of the stools, and great frequency of these, is not present, because the lesions, though frequently extensive, do not involve the rectum and the sigmoid. The pain may be colicky, but more often is constant and diffuse. The radiograph shows extensive lesions, variously situated. There may be few or very frequent motions, and the clinical picture is very similar to that described as ulcerative enteritis, which, as a matter of fact, is what it is.

We mention this form, because at times it is overlooked outside of the large endemic foci of amebic infection, and because the entamebas are sometimes not readily found, and are of the small vegetative forms. One of us (James) picked up several cases of this type in the Southern training camps, and had considerable difficulty in convincing his colleagues of the correctness of the diagnosis. The laboratory experts would not believe that the tiny entamebas were really such.

The milder cases counterfeit very closely what is described as *mucous colitis.* Patients with this type pass a varying number of glairy, mucous stools, and between attacks are constipated. The untreated condition is chronic, and an extreme degree of neurasthenia frequently develops. The disturbance is out of proportion to the colonic lesions, which have been limited in the cases we have observed.

The correct diagnosis can be made only by finding the entamebas, and this is often difficult and necessitates continued search. One of our patients had suffered for years, and had travelled over Europe and America in search of relief. Owing to his tropical nativity, amebic infection was suspected, and several times a careful search was made by well-qualified experts. The patient was under observation in Panama for three weeks, with daily stool examinations, and the diagnosis of mucous colitis would have been confirmed, had he not, at the end of that time, passed one morning a small portion of mucus containing innumerable entamebas. This type yields readily and promptly to proper treatment, in which respect it differs radically from true mucous colitis.

5. *Hemorrhages.* — Hemorrhages are not of infrequent occurrence in amebic dysentery, but they occur as well in

the milder grades of infection. Repeated and severe hemorrhages may arise from the site of a very small lesion. We have observed varying degrees of hemorrhage in several cases in which there was no history of dysentery or diarrhoea. Some of these were quite severe, and the patients were debilitated. Most of them came to us with a diagnosis of intestinal malignancy.

If the lesion is small, it may take patient search to find the parasites. All of our cases of this kind have done well under treatment.

There remains one other severe type of local invasion, which in most cases belongs to the surgeon, but occasionally yields to medical treatment. This type is characterized by an intense local infiltration with fever and prostration. It will be described by Dr. R. W. Runyan. However, we observed two cases responding to medical treatment in which both the cecum and the sigmoid were involved.

Palpable masses resembling tumors were felt over each locality, and in one case a number of mesenteric glands could also be felt. This patient was quite prostrated and, owing to the extent of the lesion, operation was not advised. Under treatment the intestinal tumor disappeared, as did the mesenteric glands. After about a month of treatment, only a very tender spot remained over the appendix. The organ was removed and found to have a chronic non-amebic inflammation. The patient returned to his home, with instructions to follow treatment and diet for at least two years. He wrote a year later that he was doing well, but recently advised us to the effect that he is now having a recurrence of his former trouble.

This complication is very serious. In one of our cases, to which further reference will be made, under treatment, which is described also by Dr. J. J. Vallarino in his accompanying paper on X-ray diagnosis, the infiltration had almost entirely closed the lumen of the transverse colon. The patient was very greatly emaciated and a diagnosis of malignancy was made. He had every indication of a severe and rapidly growing intestinal malignancy.

Further types of intestinal involvement could be cited but the above will give a fairly good idea of the many variations of this infection not at all associated with its classical fea-

tures. Our object is to point out to you how extremely variable the symptomatology of this infection may be, and how commonly it may simulate other gastro-intestinal trouble. Only careful search by those qualified to recognize the small type of *E. histolytica* will establish a correct diagnosis in many of these cases.

TREATMENT

One who is familiar with the gross and microscopical pathology of intestinal amebiasis will scarcely cavil because all cases of this infection are not permanently cured by any single system of treatment. If he practices medicine in the Tropics, rather will he be grateful for any method which will retard the progress of the disease and will allow Time and Nature to assist his efforts in bringing about a reasonable percentage of permanent cures. This is true, whether the lesions are few, resulting for the most part in unpleasant symptoms, or so severe as to threaten a fatal termination. The pathological process is in some instances one of progression, and a few small ulcers, unrecognized, or improperly treated, or both, may terminate in death. Whatever may be said for the usefulness or necessity of the large bowel, it is very certain that serious damage to it invariably is followed by grave and often deadly illness.

It is our belief that a successful treatment should attack the entamebas in the lumen of the bowel, as well as in the tissues themselves. We have evidence to show that if the luminal parasites can be destroyed, the bodily resistance will often take care of those in the tissues. But any method which will attack the organisms in the tissues is a powerful and most valuable adjuvant in treatment.

The "Tropical Dysentery" of the earlier writers was looked upon by them as a grave and serious disorder, of marked chronicity, and with an ultimate high mortality. The drugs used against the disease were numerous, but ipecac was an early favorite, and certainly cures were brought about by its use. Its alkaloid, emetin, has a marked amebicidal action, and its re-introduction by Sir Leonard Rogers in the treatment of amebic dysentery has without doubt very greatly lessened the mortality rate and reduced the number of acute cases and complications. Its chief action

is, we believe, against the tissue parasites, for reasons presently to be given.

Bismuth subnitrate in large doses was also known to act favorably in this disease. In his Lettsonian Lectures on Dysentery, in 1914, Dr. F. M. Sandwith mentions that he had used it for thirty years.

In 1908 Deeks began to treat amebic dysentery in Ancon Hospital with large and frequent doses of bismuth subnitrate, with very gratifying results. Indeed, it may be said, in all fairness, that these results were better than those previously obtained in that Hospital. Not only were they good in recent cases, but were successful in those of long standing, which had resisted other methods. The percentage of all cases of Intestinal Amebiasis could not be ascertained, because we were not then familiar with the small entamebas, and we could not follow all the cases. But in 1914 there were only 3 relapses in 190 traceable cases, admitted with dysentery during the preceding 6 years, and only 1 liver abscess.

The combined bismuth and emetin treatment is used today, without any substantial change, by Dr. R. C. Connor, Chief of Medical Clinic in Ancon Hospital, and James in the Hospital de Panama. We know of no better nor more satisfactory treatment, otherwise we should use it. An outstanding result is that among the local cases treated during the past 15 years, neither Connor nor James has at this time under observation any that have developed chronicity or that are relapsing from time to time. As far as can be determined, these cases have been successfully cured. There are about 75 of them residing at this time in Panama and in the Canal Zone.

In so far as relapse and chronicity are concerned, the dysenteric cases treated by this method have a smaller percentage of relapse than is found in treated cases of malaria or syphilis. We do not claim that all cases are cured by the first treatment; in old and chronic cases with extensive involvement of the large intestine, it is sometimes necessary to repeat the treatment, once or twice, at intervals of from 3 to 6 months. Among the local cases we have had but one, since 1914, that has resisted this treatment. This case did not improve on the first treatment, improved slightly after

the second, and was then given ipecac by mouth with very good clinical results. He went later to Ecuador where he died of liver abscess.

TREATMENT OF AMEBIC DYSENTERY

When Deeks first became attached to the Ancon Hospital in the Canal Zone, in 1906, a variety of methods were in use for the treatment of amebic dysentery. These consisted of the oral administration of castor oil, magnesium sulphate, opiates, ipecac, etc., or combinations of these; and rectal irrigations consisting of quinine in varying strengths, usually 1 to 500, thymol irrigations, 1 to 2,000 or 3,000, or combinations of both, or silver nitrate ¼%, boric acid, starch and laudanum, tannic acid, copper sulphate, potassium permanganate, normal salt solution, and plain water, warm or cold.

The table below gives the total admissions to the Ancon Hospital from the years 1905 to 1912, the number of cases of amebic dysentery, and the number of deaths which occurred.

Year	Total Admissions	Amebic Dysentery	No. of Deaths	Percentage of Deaths
1905	7,666	10	3	30
1906	13,172	55	20	36
1907	14,012	88	26	29
1908	15,378	27	5	18
1909	18,531	44	3	6.8
1910	20,122	37 (34)	4 (1)	10.8 (2.9)
1911	22,275	21	0	0
1912	21,063	41	6 (2)	14.6 (5.4)

Up to and including some months of 1908, the cases were all treated by one or more of the above-mentioned methods. In 1908 Deeks began the following method of treatment for amebic dysentery:

First: Rest, in order to increase the patient's resistance and give the minimum of movement to the bowel. This is classical treatment in all acute infections.

Second: A generous milk diet. This, because it is a physiologically nutritious diet, admits of a minimum of intestinal putrefaction, and is practically all absorbed before it reaches the large bowel, which, owing to its ulcerative condition, is more or less physiologically inert.

Third: Saline or plain water irrigations 1 to 3 daily, purely for the purpose of lavage, in order to rid the bowel of toxic products.

Fourth: The administration of bismuth subnitrate in heroic dosage. We give a heaped teaspoonful, equivalent to about 180 grains by weight, mechanically suspended in almost a tumbler-full of plain, or better still, effervescent water, or in milk, every 3 hours, night and day in severe cases, lessening the amount only when improvement takes place. The mechanical suspension in a large amount of water or milk is essential, — otherwise the bismuth is prone to form a paste or solid mass, thus lessening its physiological effect. When the stools begin to become fewer, and the tongue becomes clean, the number of doses is reduced to 4 daily. In very chronic cases it is wise to continue 3 or 4 doses daily for 2 or 3 months after convalescence is established.

The absolute milk diet is not departed from until the tongue clears, the tenderness over the bowels disappears, the elasticity of the skin returns to normal, and the stools have been reduced to 1 in 24–48 hours; then a normal diet may be gradually resumed, as in convalescence from typhoid. Plain fruit-juice, once or twice a day, instead of the milk, is recommended during the acute attack. We do not object, at the beginning, if tenesmus and distress be severe, to an occasional hypodermic of morphine and atropine, but as a routine measure it is not considered good treatment. At present, we do not believe that saline irrigations are necessary except in those cases in which ulcerative lesions are near the rectum and associated with tenesmus.

This method of treatment gave us exceedingly satisfactory results from 1908, as can be seen by the above table, showing the reduced percentage of deaths after the institution of this treatment. It will be noted that there were 4 deaths in 1910, and 6 deaths in 1912; 3 in 1910 and 4 in 1912 were admitted either in a moribund condition or complicated with other serious conditions which were primarily responsible for their death, and none of them received more than 2 or 3 days of bismuth treatment.

In 1912, Rogers introduced emetin, and in 1914 we began its use in the Ancon Hospital. During that year we treated

12 cases by emetin alone, and of the 12 cases we had a definite record that 6 relapsed in from 3 to 6 months. In the report of these cases, published in the "Annals of Tropical Medicine and Parasitology" in July, 1914, Deeks stated that he believed that emetin acted as a direct poison to the entamebas, in the same manner as quinine does to the malarial parasites, and we are still of that opinion. In acute, fulminating forms, there is no drug in our experience which gives the brilliant results produced by emetin hydrochloride. We do not believe, however, that it is entirely efficacious in chronic forms of the disease.

Since 1914, we have combined the use of emetin hydrochloride with the bismuth-subnitrate method outlined above. The emetin is administered in from ½ to 3 grains a day until the limit of tolerance is reached, and coincidently with this we begin the use of the bismuth subnitrate.

Rogers recommends the following method of emetin administration:

> To get the best results, I find it is advisable to inject a total of 1 grain in the 24 hours for 3 or 4 days, preferably in ½-grain doses morning and evening. In severe cases I frequently give a grain at a time (this being equivalent to 90 grains of ipecacuanha) and repeat it 2, or even 3 times a day, although this is not often necessary. Intravenously from ½ to 1 grain may also be given at a time with perfect safety to adults. It is also surprising what large amounts may be given to children, for I have several times injected ⅓ grain (equal to 30 grains of ipecacuanha) in children of about 8 years of age with amoebic dysentery, with excellent results, while ⅙ grain may be given in still younger patients.
>
> The local effects of the injections are usually slight, the salt being rapidly absorbed. Very occasionally a considerable amount of pain has been noticed for a few hours, possibly due to injection near some small nerve. Either the upper arm or the flank is convenient for injections. If given by mouth in tabloid form, it is advisable to use doses of not less than ½ grain to 1 grain to get a full effect quickly.

In 1915 Deeks took charge of the work of the Medical Department of the United Fruit Company, and since that time this combination method of treatment has been in use in all the hospitals under his direct jurisdiction. The following table gives the number of total admissions to the hospi-

tals, the number of amebic dysentery cases, and the percentage of deaths, since that time. This includes all cases, some of which were admitted in a moribund condition or complicated with some other serious condition directly responsible for the fatal termination. It will be noted that in this table, as in that above, only the various forms of amebic dysentery itself are included. We are unable to present accurate data as to the amount of amebiasis without dysentery that may be included among the total admissions in both tables.

Cases

Year	Total Admissions	Amebic Dysentery	No. of Deaths	Percentage of Deaths
1914	15,535	258	16	6.2
1915	13,583	476	24	5.0
1916	11,847	216	12	5.6
1917	12,259	185	4	2.2
1918	12,896	189	7	3.7
1919	21,732	276	6	2.2
1920	25,259	215	9	4.2
1921	26,337	170	13	7.6
1922	26,646	262	5	1.9
1923	28,398	420	7	1.7

During this entire period (1914–1923, inclusive) 95 cases were admitted to the hospitals with liver abscess, and 17 of them died (18%).

During Deeks' experience in the Canal Zone we were able to follow 66 treated cases over a period of several months, and found that we had 4½ per cent of relapses. In several of these patients the physical condition was low from some other complicating infection. Unfortunately, we are not in a position to give any definite information concerning the number of relapses which occurred in the United Fruit Company hospitals.

How does bismuth subnitrate act? In 1883, Theodore Kocher demonstrated that the insoluble preparations of bismuth were actively antiseptic to fermentative and putrefactive bacteria. It is further known, clinically that on the mucous membrane of the intestine bismuth has a local sedative and astringent action. In our former paper we suggested that the curative power of bismuth subnitrate in

amebic dysentery rested largely on its antiseptic properties against the putrefactive and fermentative bacteria. Now, however, we are led to believe that the process is more elusive than we had anticipated.

Dr. S. T. Darling has shown that the bismuth salt locks up the free sulphur on the surface of its crystals, and even seizes upon the nuclear sulphur of the bacteria, turning them very black. It also affects the general flora of the intestines, destroying certain organisms and influencing others. In some manner it eliminates some essential, either in the food supply or in the environment of the highly susceptible entamebas.

James has shown that the bismuth salts have an indirect influence on the entamebas, and also on the bowel contents (which we have frequently observed and directed attention to) not only destroying the characteristic odor, but liquefying the stool by ridding it of the mucus through liquefaction or inhibition of its production.

The entamebas show early degenerative changes. They become vacuolated, swell up, and the nuclei disappear. In 2 instances only in our experience (James) have entamebas been observed in the stools after 4 days' treatment by the bismuth method, no matter how grave the condition was when the treatment was begun. In one of these cases entamebas were found alive on the 5th day, but not afterwards; and in the other case, after disappearing on the 3rd day, they reappeared again on the 8th day in large numbers, evidently from the discharge of an entamebic abscess from the intestinal wall, as the patient afterwards made an uninterrupted recovery from the dysentery, but returned 2 months later with a liver abscess.

Our present belief is that certain products of putrefaction are essential to the life of the organisms, and that bismuth acts either in destroying the putrefactive bacteria or in neutralizing some product of putrefaction essential to the existtence of the organism: (Simon states sulphuretted hydrogen, which is a product of putrefaction, is necessary to their development. This is converted by the bismuth salt into the sulphide of bismuth). It is quite possible that an infection in the appendix or in one of the submucous abscesses can persist for a considerable time uninfluenced by the drug,

and be responsible for a later relapse. Untoward effects of bismuth subnitrate in doses referred to above occasionally happen, and the patients become cyanotic, but with full pulse and heart action. This is due to the use of impure bismuth, and is not seen when a chemically-pure drug is used.

Although the symptoms may be alarming, they disappear rapidly after a dose of magnesium sulphate. That amebic ulcers do heal under this method of treatment, Dr. Clark has fully demonstrated in patients who died subsequently to initiation of this treatment, or in cured cases who later died from some other cause. In patients who died after the initiation of treatment, active pink granulations were found running out from all the islets and strands of the mucosa not destroyed, which in some cases quite filled the ulcer.

In the older cases cicatrices throughout the cecum and the rectum, of the healed amebic type, were found. These healed cicatrices are stellate, pigmented, somewhat depressed and contain a lace-like collection of arterioles (according to Dr. Clark) and the healed mucosa seems to function. It is stated above that the appendix is frequently involved, and it is the only place in which Dr. Clark has been able to find amebas at the autopsy of cases who had taken bismuth. This is interesting, because the appendix is sometimes almost inaccessible to the bowel contents which filter in from the cecum. The lesions in the cecum, however, are more accessible to treatment, and heal before the lesions in the appendix, where the putrefactive bacteria can subsist only as long as suitable pabulum is provided for them from the cecum. When this is rendered unavailable and cannot be further supplied, then the amebas are destroyed.

Relapses. Out of 100 cases of liver abscess admitted to the Ancon Hospital, in 2 cases only had the bismuth method of treatment been administered during a previous hospital admission, and one of these had been treated for only 3 days. A case was admitted on March 7, 1912, received the regular routine bismuth treatment, and was discharged on April 23, but during the last 2 weeks in the hospital had been running a slight temperature. On June 18, he was re-admitted with a liver abscess of the benign type. It is probable that the liver infection was present when he was discharged from the hospital in April.

Judging from our clinical experience and the pathological evidence, cases of dysentery are usually cured with few relapses, and rarely the development of a metastatic abscess. In all acute cases the course of treatment is materially shortened and the probabilities of cure greatly increased by the administration of bismuth subnitrate, and it is particularly indicated in chronic relapsing and in latent cases.

Other Methods Recommended for Treating Chronic Amebic Dysentery. — A number of authorities still recommend the use of the powdered Brazilian ipecac root which is made up fresh in 5-grain pills, subsequently coated in melted salol, and administered daily in doses of from 50 to 75 grains at bed time, until about 500 grains are given. The chief objections to the ipecac are: (1) that it frequently causes severe vomiting; (2) a great many patients cannot swallow pills of this size; (3) frequently pills are passed without being absorbed; and (4) the results are uncertain. Some form of mild laxative is recommended as useful before the administration of the ipecac, and the patient is put on a strictly liquid diet excluding milk. To overcome the nausea or vomiting, morphine (1/8 to 1/4 grain) or tincture of opium (10 to 20 drops) is administered half an hour prior to the administration of the pills. Phillips recommends the addition of tannic acid (1/2 to 1 grain to each pill) for the same purpose.

Chapparo amargoso is also recommended by some authorities, either in the form of the liquid extract (1 to 2 teaspoonfuls 3 times daily before meals) or as an infusion in from 6 to 8 ounces 3 times a day before meals.

Infusions of *simaruba officinalis* have also been used with varying results. We may also mention the use of the compounds — emetin-mercuric iodid, emetin-bismuth iodid and methyl-emetin sulphate; also alcresta tablets, a trade-name for a preparation of the ipecac alkaloids with Fuller's earth. The reports on the results from the use of these preparations have not been sufficiently encouraging to justify us in adopting them.

German authorities also recommend highly the use of a preparation called Yatren, but we have had no experience with it.

We have tried the salvarsan preparations administered by the bowel, without obtaining any satisfactory specific action

on the pathogenic amebas. They will kill the entamebas that they reach, but many escape. Bayma recommends the use of adrenalin in from 10 to 20 drops of a 1-1000 solution, by mouth, every 2 hours, but from what is known of its physiological properties we do not see how this can have any amebicidal action.

The uniformly good results which we have obtained by the combined use of emetin hydrochloride hypodermically and of bismuth subnitrate after the manner indicated, have justified us in continuing to apply this routine method, as the results reported by different authors regarding the use of other remedies have not warranted us in adopting any of them for general use in our hospital services.

Reference has been made to the effect of this treatment in a severe case of intestinal infiltration. Another case also deserves especial mention. The patient was admitted to the Hospital de Panama in an advanced state of debility due to malnutrition. A tumor running from one side of the abdomen to the other could be palpated over the site of the transverse colon, as could numerous mesenteric glands. The X-Ray showed a great filling defect with an almost complete stricture.

Frequent and repeated examination of the stools failed to show any entamebas. The Wassermann reaction and other tests did not give any information. An exploratory operation was advised, but refused. A diagnosis of cancer of the transverse colon was made, although an amebic condition had been suspected. Before any treatment could be given, the patient left and went to Ancon Hospital, where he was admitted to the medical service under Dr. R. C. Connor. Here, also, repeated searches for the entamebas gave no results, and a malignant condition was strongly suspected. After about 2 weeks *E. histolytica* was found in a mucous stool sent to the Board of Health Laboratory. The patient was put on an intense emetine and bismuth treatment with marked improvement. He gained in weight, and the infiltrated mass subsided; 2 months after the treatment had been started he was in excellent health. He returned to his country about a year ago, and we heard recently from one of his relatives that he had improved greatly.

There are certain essential factors in this treatment which

must be followed strictly, whether the case be one of mild amebiasis or a severe dysentery itself. Intestinal ulcers, although they heal readily under favorable conditions, do not heal within 1 or 2 weeks, and the more severe the ulceration, the longer the time that will be necessary for healing to take place. All the acute symptoms may, and often do, disappear within a few days, and within 10 days or 2 weeks — even in cases of severe dysentery — the patients will feel as though they need no further treatment.

For several years it has been our practice in the milder cases of amebiasis, with or without dysentery, to insist upon a liberal but non-irritating diet for 2 or 3 months, and we continue the use of the bismuth for at least 6 weeks after the stools are normal and the symptoms have disappeared. In the severer cases, the same treatment is followed from 2 to 4 months. During the first 10 days of the treatment a very strict diet must be followed. It does not appear that food itself is harmful in these cases, but if a solid or semi-solid diet is given in the early stages of the treatment, the action of the bismuth is very much diminished. Under these conditions a very large percentage of the bismuth becomes mixed with the intestinal contents and loses the marked amebicidal effect which it has when the large bowel is as empty of food as possible.

These factors in the treatment are frequently overlooked.

This treatment is essentially a hospital one, and should be given only under hospital control or under the care of an efficient nurse. Left to themselves, patients will not follow it properly. It has been very apparent to us that better results are obtained when emetine is given in increasing doses to the point of toleration. However, it is not a practice to recommend, unless great care is taken. Emetine is a powerful cardiac depressent, and also acts at times as an active nerve poison. A great variety of symptoms result from overdosage, — amongst them, localized as well as multiple neuritis, the latter sometimes resembling in its manifestations those seen in beri-beri.

At times very considerable muscular weakness also develops. Stomatitis has occurred several times in our cases. Fortunately, these effects are temporary and clear up within 1 to 3 weeks. One factor in the use of emetine must be care-

fully borne in mind. It should never be used, except in urgent cases, even in small doses, if surgical intervention is contemplated, especially that involving the use of a general anaesthetic. We speak here from personal experience.

If, in urgent cases — such as acute dysentery with development of a liver abscess during or shortly after the emetine treatment — an operation is necessary, the heart should be very carefully examined. The principal dangers during and after an operation are cardiac failure and paralytic ileus.

However, the treatment can be safely given during convalescence from an operation, and it is our practice to give it then. We have frequently had cases in which the amebiasis was coincident with conditions entirely apart from it, such as non-amebic appendicitis, gall-bladder trouble, myoma, and many other surgical conditions. We have never had any trouble when this treatment was given with proper precautions, after convalescence from a surgical operation has been well established.

Conclusions

1. Intestinal amebiasis is one of the most widely spread and most frequently encountered tropical infections.

2. The symptoms, for the most part, vary according to the extent of ulceration in the large bowel, but small localized ulcerations may give rise to very marked symptoms.

3. The extent of ulceration cannot always be determined by the physical examination in any given case. There may be extensive involvement of the large bowel without dysentery. We believe that the X-Ray will be of considerable service in determining the extent of ulceration.

4. The extent of intestinal invasion must be taken into consideration in the treatment of these infections. Time must be allowed for the ulcers to heal, and in some cases from 2 to 4 months of treatment are necessary.

5. The symptomatology, apart from the dysenteric manifestations, is very complex, and may imitate almost any gastro-intestinal disturbances. Complications are numerous, and often render the diagnosis difficult. Only one who is thoroughly familiar with all phases of the life cycle of the intestinal entamebas of man, can arrive at a correct diagnosis under these circumstances.

6. We believe that the bismuth and emetine treatment, as above described, if properly carried out, will cure a very large percentage of cases.

7. Emetine is a drug which must be used carefully, and never (except in urgent cases) when a surgical intervention is under consideration. It can be given safely during convalescence from operation, provided that its administration is carefully watched.

8. It is a most favourable drug in the treatment of acute amebic infection, but rarely effects a complete cure unless combined with other methods of attacking the parasites. This is probably because its action, for the most part, is against the parasites in the tissues, and it does not effect a complete elimination of the luminal parasites.

9. Bismuth subnitrate, when used alone under proper conditions, will bring about a cure in a large number of cases. Its action, however, is enhanced by the simultaneous administration of emetine. The action of bismuth subnitrate against the entamebas is due to some unknown change effected by it, in the environment of the parasites, — which reacts unfavourably against them.

10. The bismuth treatment, alone or in combination with emetine, is essentially a hospital treatment, and to be successful must be given under conditions of strict control with respect to dosage and diet.

THE ACCLIMATIZATION AND THE FREQUENCY OF AMEBIASIS IN THE LYON REGION IN FRANCE. TWO NEW ARSENICAL COMPOUNDS AGAINST AMEBIASIS: STOVARSOL AND ACETYLARSAN

Ch. Garin, M.D., and Pierre R. Lépine, M.D.

The invasion and the progressive establishment of Amebiasis in France, is already an old subject of discussion.

Before the World War — as far back as 1905 — Dopter had already shown that this infection had been distributed by interhuman contagion amongst colonials reëstablished in France.

The fixation of this disease in France had been noticed in all districts: in Paris, by Galliard, by Menetrier, by Lesage, and above all by Chauffard; in Marseilles, by Billiet; in Lyons, by one of ourselves, and also by Paviot and Garin, by Cade, Thévenot and Roubier.

During the World War the importation of amoebae from the hot countries, was considerably increased by the utilization of colonial troops on French soil. Of the numerous researches of inquiry into this invasion, we shall note those of greater importance: those of Ravaut and Kronulitzky; of Richet, Jr.; of Bouyer; of Ameuille and Tillaye; of Leboeuf and Braun; of Cade and Vaucher; of N. Fiessinger and Leroy; of Mattei; of Charpin; of Bonnamour and Chapuis; of Hanus; of Bouchut and Bonafé; and of Leclerc.

It appeared to us to be interesting to try to determine whether the invasion of *Entamoeba dysenteriae* in France, and particularly in Lyons, had continued incessantly, or had been subject to breaks since the end of the World War.

Since we found it impossible to extend our search into the private practice of all the doctors in the region, we shall confine ourselves for the moment to outlining the result of an inquiry into 208 cases of Amebiasis. Among these, 197 are gathered from the private practice of one of ourselves, from

the year 1920 to 1924. We are indebted to the kindness of Professeur Agrégé Cade, Médecin des Hôpitaux, for the details of 7 cases that we have added to our own.

The existence of such a number of these cases (208) in such a limited group, makes it obvious that in the Lyons region this disease is by no means rare. Of these 208 cases, 191 are male, and only 16 female. We have observed only one case in a child. To deal with the *place of origin* of the cases, we give the following tables:

TABLE I

A. *Exotic origin:* 168 cases, of which 157 were male and 11 female.

	Male	Female
Army in the Orient, Macedonia	73	..
Indo-China	32	5
Morocco	23	2
French Central-Africa	7	..
Egypt	5	1
French West-Africa	4	1
Syria	4	..
Tunis	3	1
Madagascar	2	1
South Algeria	2	..
French Somaliland	1	..
French Guiana	1	..
	157	11

TABLE II

B. *French origin:* 40 cases, of which 35 were male, and 5 female.

	Male	Female
Individuals having come more or less into direct contact with colonial troops during the war	21	..
Infection probably produced by some member of the family, other than husband or wife	3	..
Infection produced by husband or wife	..	4
Infection of indefinite origin	11	1
	35	5

A study of these two tables shows the importance of the exotic origin of this disease in the European cases: 81 per cent of our cases were contracted in the tropical countries, and only 19 per cent of the infection took place on French soil.

If we examine more closely the 40 cases in which the disease was contracted on French soil, we see that 21, or 52.5% were contaminated by contact with the colonial troops. These figures, without having a very great significance, nevertheless show in a striking manner the grave importance of the tropical importation of amoebic infection into our region. We find the infection of women by their husbands amounts to 10%, which is a very high figure when we bear in mind that many of our patients are unmarried.

If we now consider the cases due to direct interhuman infection that we have been able to examine, and compare them with the cases of unknown or indefinite origin, we observe that the interhuman infection produces 72.5% of the cases. That shows the preponderence of this means of infection by Amebiasis as compared with the other means suggested, such as infection originating from impure water and the carrying of the germs by flies or in dust.

From the viewpoint of *prophylaxis*, we are taught by the examination of these statistics that all the countries in Europe should carefully watch the entrance of immigrants and of those who are repatriating themselves from the tropical countries. It is certain that proper restrictions against possible carriers of amoebae at the frontiers and ports of entry, will greatly diminish, and perhaps even suppress, Amebiasis on French soil. Amebiasis, as well as other exotic diseases, such as leprosy and, above all, trachoma, presents a problem that the public authorities should solve.

If we consider, now, not the number of the cases of Amebiasis, nor their origin, nor their prophylaxis, but their *severity*, the results of the examination of our cases permit us to make the following statement:

The cases with *hepatic complications* that we have noticed, are 6 in number: 2 abscesses of the liver, which developed in Indo-China; 1 other from the army in the Orient during the World War; and 3 in France, of which 1, an autochthonous case, was followed by death, while the other 2 were cured.

We also observed an abscess under the tibial periosteum in this patient, infected in France, who died from an abscess of the liver.

Pulmonary Complications. — We have observed only one case of broncho-pneumonia, developed by a patient contaminated in Indo-China, and complicated in France by an abscess of the liver.

In an autochthonous case other than the one mentioned above, we have noticed a remarkable complication. The patient, who was neither syphilitic nor uremic, nor afflicted with any aortic trouble, suffered mainly from chronic diarrhoea, but also had irregular attacks of acute oedema of the lung, with a choking sensation. Fine râles were heard all over his left lung, and his expectoration was slightly blood-colored. This expectoration did not contain amoebae, but the attacks yielded to a treatment with emetine.

The very small number of complications observed, as well as the slight intestinal manifestations in our patients, permit us to say that Amebiasis in our region, although common, is not a very serious disease. This is due principally to the efficacy of the treatment; and it is possible, also, that the climate plays an important role. Most of our cases are those of chronic diarrhoea, and recurring colitis with dysenteric periods.

Although Amebiasis in our region does not appear to be a serious disease, it is none the less a chronic complaint recurring with great insistence in spite of regular treatment. The relapses are usually most frequent during the first hot months of the year, *viz.*, June and July, and also during the autumn months — September and October.

Among the notable peculiarities of the *evolution* of Amebiasis in our region, we have been impressed, like others who have gone into the subject, by the frequency of the anaemia. We cannot give exact data in regard to this anaemia, for we have carried out a blood count in only 28 of our cases. In one of these cases, the red-blood corpuscles were reduced to 3,000,000.

Another point to which we should like to draw attention is the frequency of injury to the adrenal glands and to the solar plexus, in the long-standing cases of Amebiasis. In 44 of our cases (22%), we have found that these organs have

been affected. In these cases the feces never, or only rarely, contain amoebae. These patients have a chronic diarrhoea, sometimes liquid accompanied by colic, and are not responsive to either the emetine or the arsenical treatments.

Their systolic blood pressure is often below 120, and they are always remarkable for their thinness and their palour. Pigmented patches and browning of the skin have been noticed, but are less frequent. The administration of adrenal extracts, or of adrenalin, to these patients, does not always give entirely satisfactory results. In one solitary female case of this type of diarrhoea, the administration of adrenal extracts, together with adrenalin, gave us a surprisingly quick result, after the failure of the amebicidal treatment.

We can also give you a few details concerning the *associations of parasites* with which we have met in the course of the examination of the feces:

TABLE III

Association of parasites:	Cases
with *Lamblia intestinalis*	11
with *Lamblia* and *Trichomonas*	7
with *Trichomonas intestinalis*	3
with *Spirochetes*	22
with *Helminths* (*Oxyuris*, *Trichuris*, *Ascaris*)	15

We must repeat, with the established authors, that Amebiasis associated with *Lamblia* or with *Trichomonas* is found in some cases to be especially resistant to emetine.

Against *Lamblia*, Stovarsol and Acetylarsan have alone appeared to us to be effective. Also, in the cases associated with Spirochetes, we have noticed a very strong resistance to the amebicidal treatment, even when emetine is administered with the most efficacious arsenical drugs. The employment of iodized oil, and especially Lipiodol, has been found very useful; but only in a small number of cases was it used. Owing to the incompleteness of our investigations into this matter, we are unable to say, with any degree of certainty, what role these Spirochetes play in the disease. We are still studying the question.

We have also observed some *clinical associations* of Amebiasis with other diseases, in the following number of cases:

TABLE IV

Clinical associations:	Cases
with active pulmonary tuberculosis	8
with active pulmonary and intestinal tuberculosis	4
with chronic malaria	128
with active malaria	3

From this table we draw no definite conclusion.

In commenting upon the *treatment* of Amebiasis, we do not intend to refer to emetine, the different uses of which are already well known. But it is also known that certain cases resist emetine, and it is this fact that led to the adoption of other treatments, especially the use of arsenical drugs.

Until recent years, Novarsenobenzol employed for intravenous injections seemed to be the only efficacious remedy. As a result of our own investigations, however, we should like to draw your attention to two new arsenical compounds: Stovarsol and Acetylarsan.

Stovarsol is administered by mouth, in pills of 25 centigrams, either alone or dissolved in water. The latter method we believe is the better.

This remedy, the efficacy of which has been recognized by Marchoux, Delanoe, Fontanel and Milischer, Cade and Garin, may be employed either alone or associated with emetine.

The combined treatment of Stovarsol with emetine lasts for 4 weeks, and consists of the administration of 50 centigrams of Stovarsol a day during the 1st and 3rd weeks, and the administration of emetine during the 2nd and 4th weeks.

The "opening" treatment, or "traitement d'attaque," with Stovarsol alone consists of the administration of 75 centigrams per day for 1 week, this being discontinued the following week, with the continuation of the daily dose the 3rd week.

These "opening" treatments should generally be followed by a treatment for maintaining the effect, for 1 or 2 months, by the administration, every other day, of 25 centigrams of Stovarsol.

Such treatment is but slightly toxic, and the inability to take this drug is rare. We have never noticed detrimental effects that could be attributed to the drug.

If its action is followed up by examination of the feces, it will be seen that the Amoebae disappear in 4 days. The cysts disappear, in their turn, from the 8th day of the treatment. *Lambliae* are also affected by Stovarsol, and from this point of view that drug appears to us to be superior to Novarsenobenzol. On the other hand, *Trichomonas* resist it.

Acetylarsan is another drug that is, as yet, little known. It has been studied as an anti-syphilitic by Ch. Laurent (of St. Etienne). We have employed it with very great success in Amebiasis.

Acetylarsan is a white crystalline substance of stable character, readily soluble in water, and possessing practically no local irritating action. It is put up in phials of 3 cubic centimeters, each cubic centimeter containing a solution of 25 centigrams of Acetylarsan, *i.e.*, 75 centigrams in each phial. The contents of the phials may be injected subcutaneously; and, with a better result, into the muscles. These injections are painless, and the drug is but slightly toxic.

This has been employed by Garin, without the use of emetine, in a case of hepatitis, with remarkable success. The dose was 75 cgrs., once a week for 4 weeks.

The treatment of Amebiasis with Acetylarsan and emetine combined, must be conducted in the following way, and must last four weeks: Emetine is administered the 1st, 2nd, and 3rd day of each week; the 4th day, Acetylarsan is administered in a dose of 75 cgrs.

The "opening" treatment with Acetylarsan alone consists of a primary injection of 75 cgrs.; 3 days later a 2nd dose of 75 cgrs.; and a succession of injections of the same dose at intervals of 8 days until 6 or 7 doses have been administered.

Following up the action on the parasites, by examination of the feces, we have observed that the Amoebae disappear rather slowly after the 8th day. The cysts disappear at the same time, and in the same way.

Lambliae are very much affected by Acetylarsan, and disappear the morning following the first injection.

Trichomonas in the only case which we have had cause to treat, have likewise disappeared after the first injection.

In conclusion, Stovarsol and Acetylarsan appear to us to be the most desirable arsenical drugs to adopt in the treatment of Amebiasis. They are easier to administer, and less toxic, than Novarsenobenzol, and are also much more effective.

DISCUSSION

Sir Leonard Rogers (*Opening the Discussion*). — Among the numerous points raised in these important papers, permit me to refer to a few. In the first place, I am glad Dr. James laid so much stress on the clinical variations of amebic diseases of the bowel which include extremely acute types with great thickening of the bowel, while enabling tumor-like masses to be felt and requiring very urgent emetine treatment to save their lives. Cases vary from the acute type to all stages down to chronic diarrhoea without dysenteric symptoms, the true nature of which is so often overlooked, although most chronic diarrhoeas in India are really amoebic in nature.

Dr. Lepine in his interesting paper brings out the number of infections through association with carriers in a way which is difficult to trace in much-infected tropical countries, though coming out clearly in slightly infected areas of France where he worked.

With regard to treatment, I note that Dr. Lepine advised the use of arsenical preparations first and emetine afterwards, which is probably effective in the mild types which he met with, but I do not think this would be safe in very acute types met with in the Tropics in which the emetine should be given first.

It is a difficult question regarding the treatment of relapsing dysentery, in which I have found a few injections of emetine followed by large doses of ipecac orally and subsequent administration of small doses such as 5 grains of ipecac every evening at bedtime for two months or more sometimes prevents further relapses. In cases resisting the emetine treatment I have found Dr. Deeks' method of giving large doses of bismuth subnitrate to be effective, and I regard his method as an important advance.

Dr. Roland C. Connor. — Dr. James, Dr. Lepine, and Sir Leonard Rogers have covered about all that I could say, except in regard to the question of treatment of amoebiasis, simple amoebiasis, wherein there is no definite history of frequent, or any prior, attacks of dysentery. Such condition is a frequent occurrence and, as Dr. James tells you, we attribute many of their symptoms which we cannot otherwise explain, to the amoebic infection. Personally, I am inclined to the view that an amoebic infection might have

some of the same relations to a man's debilitated condition that chronic malaria would have. I believe that in cases in which we find cysts of *Entamoeba histolytica* without definite histories of previous attacks of dysentery, there is a focus of ulceration somewhere in the large bowel. It is hard to conceive that the *Entamoeba histolytica* would remain free in the intestinal tract and among the feces, and not at some time invade the tissues of the bowel at some point. These cases are very difficult to treat, and even to diagnose from the clinical laboratory standpoint, because cysts of other amoebae are commonly encountered in the routine stool-examinations, which are of no clinical importance.

How are we going to differentiate, without special training in such work, cysts found in the stool of a well-nourished individual who has various complaints possibly due to amoebic infection? How are we going to tell whether or not they are the cysts of *Entamoeba histolytica?* I must say that our dependence on laboratory men in this respect has been very disappointing. It is my firm opinion that a laboratory man, to give you always a definite answer in the majority of your cases, has to be one of broad experience in this line of work, and that you cannot depend upon an inexperienced laboratory man to differentiate cysts correctly.

There is also the question of keeping a patient in the hospital for from 3 to 6 weeks, and treating him for a disease of which he may have no symptoms except your suspicious findings in the stools. Of course, there is no doubt what our duty is if we are certain that the patient is infected with *Entamoeba histolytica;* but I want to call your attention to the necessity of accurate differentiation. A stool containing cysts is frequently encountered. This is especially so among the poorer classes, and sometimes in the more wealthy class, such as cattle ranchers who live in the interior of Panama with the native laborers and are often in contact with them.

Another point on the administration of emetine, the dose, and the frequency of dosage: — As Sir Leonard Rogers has told you, in his experience — and we are all of the same opinion — there are cases in which the emetine seems to do some good, but the cases go along with the dysentery just the same. In 2 such cases I have given ipecac by mouth with apparently good results, but not a cure. The markedly depressant action of emetine I have seen in only a few cases. I rarely hear a complaint about it.

Formerly our routine treatment with emetine was in small doses — $\frac{1}{3}$ of a grain twice a day. Later I advocated a dosage of 1 grain daily for from 9 to 12 days, as given by the English working in northern Africa. Now I rarely give over 9 grains in one course

and have decided that in many cases it is possibly better to give emetine intermittently. You may give a dose of 1 grain to a man of 125 pounds or over, but to smaller people or to a debilitated person less should be given. We give routinely 1 grain a day for 3 days, then allow 3 days to elapse before repeating the treatment for 3 days — and so on until 9 grains are given. This takes about 15 days, and that is about the number of days I want my patients kept quiet. I also keep them on a liquid diet, milk only if possible, for about 10 days.

When an intelligent patient comes from a distance, I advise him, and write to his family physician, that the emetine and bismuth treatment should be repeated at the end of 6 or 8 weeks from the time he leaves the hospital, hoping, of course, that in this way we may prevent relapse.

Soon after Dr. Deeks advocated massive dosage of bismuth, I found that a majority of cases failed to reveal motile amoebae after 24 to 48 hours of bismuth treatment. That was one of the most striking features, to me, on which I judged the efficacy of the bismuth treatment. It seemed to free the intestinal contents of amoebae. I understood Dr. James to say that prior to surgical interference (I suppose he alluded to liver abscess) he would not advocate administration of emetine. That is the opposite to the view that I have taken. I advise surgeons — when I am requested to see such a case and make a diagnosis of amoebic hepatitis — to treat with emetine first and, of course, later on if necessary operate.

I would go further, and say that if I know there is a large abscess in the liver and am called to see the case, I advise emetine for at least 2 days before operation or needling. That would, of course, depend on the emergency of the case. I believe the effect of emetine is so certain and striking that the probability of recovery after drainage is better if the emetine be given before, rather than waiting until after, the abscess has been drained.

Sir W. Arbuthnot Lane. — If you will excuse me as a mere surgeon, I would like to say a few words as to the surgical treatment of intestinal amoebiasis.

There is in London at the present moment a Dr. Jackson, who had for 20 years a large practice in Indo-China. He left there four partners who send him home a regular supply of dysenteries which have resisted the most thorough treatment. During the last few years Dr. Jackson has become thoroughly familiar with the pathology of, and with the method of dealing with, chronic intestinal stasis. He was soon able to satisfy himself that the factor which prevented the cure of such cases by medical treat-

ment was the obstruction that was afforded chiefly by the "first and last kink." By the division of this kink and any other secondary kinks we were able to cure a number of these cases in a remarkably short time.

Some of these cases were complicated by an inflammation of the iliac colon which involved the "first and last kink," and which rendered it impossible to satisfactorily divide the kink and to cover over the raw surface left. In such cases the division of the ileum, and its introduction into the side of the pelvic colon, at once effected a cure. We have had some remarkable cases. A lady who had been passing blood and mucus for 14 years, who was wasted and who vomited freely, within 2 months went away 2 stones heavier, and later we heard that she had gained still more weight. After the operation of ileo colostomy she became a perfectly normal, healthy woman.

I think it is exceedingly important that you medical people should sufficiently recognize the very important part that stasis plays in the chronic dysentery in the white subject, and that when paraffin and the other medical means which we use to counteract stasis fail, operation by some competent surgeon should be resorted to. The indications for operation are as clear and as definite as possible, and I know nothing more nearly approaching a miracle than the benefit which results, in chronic amoebic dysentery, within a few days from the freeing of the colon from the bands that control its effluent.

There are so many physicians here who have such a lot to say that I will not detain you any longer, but I would urge you to give the surgical aspect of dysentery your most careful consideration.

Dr. Friedrich Fülleborn. — I would like to ask the members of the Conference whether it is possible with a simple chemical method to sterilize fresh, green lettuce against amoebic cysts in the same manner as it is possible to sterilize against bacteria which do not produce spores (typhoid, cholera, bacillary dysentery, etc.) with a solution of calcium hypochloride, since all the *mechanical* washing with water is not effective enough because the germs remain attached to the sticky surface of the leaves. The eggs of the helminths attached to the leaves will practically be impossible to get rid of with chemicals, but they are not so dangerous as bacteria and amoebic cysts.

I personally never eat green lettuce in the Tropics because one can very seldom be sure that it is not contaminated with human manure (and for this reason I do not allow it to my patients in the Tropics); but the physician quite often would like to order fresh lettuce as a diet, not only in scurvy, but also in other cases.

Dr. Foster M. Johns. — There is not very much which I can add to the discussion of the treatment. I have some very definite ideas regarding the pathogenicity of amoeba, particularly in regard to the question that Dr. Connor raises. It is very striking, to the clinician at least, that there must be many cases of *E. histolytica* cyst-carriers that have never had an acute dysentery and, when observed for months or years, do not develop lesions.

I have some cases in private practice that I examine from time to time, and when I wish to demonstrate cysts to students these cases never fail to furnish material. The cysts from non-diseased carriers have failed to produce acute disease in baby kittens (nurslings), while the acute disease may be produced at will with cysts only (so far as I can determine) from dysenteric cases. The morphologic differentiation of pathogens from saprophytic cysts, to me is therefore doubtful.

The treatment of the acute amoebic lesions is probably divided into 2 parts. It is very easy to see that a gross lesion will require some medication that is either absorbed from the bowel, or is given intravenously or hypodermically. Following eradication of the vegetative endamoeba from the depths of the lesions, the relapse must occur undoubtedly from the surface, and I am confident that that is where bismuth subnitrate is efficacious, in a mechanical way principally.

I was very much impressed with the clinical results of Dr. Deeks' treatment, which I followed several months in Panama. In order to determine to what extent it was efficacious, we followed several cases under treatment with massive doses of bismuth, by removing material directly from the lesion, through the proctoscope, and found that there was no demonstrable diminution in the number or appearances of the endamoeba. I believe that it acts as an inert mechanical agent protecting the damaged epithelium, and thus promotes healing and the recurrence of the disease following the relief of the acute symptoms by emetine.

Dr. Aristides Agramonte. — I have not very much to say about the treatment of amoebiasis. With reference to infection, of course we all agree that it is an oral infection with the cysts, but it might be of interest to the Conference, from a sanitary standpoint, to know what occurred with us when the United States took charge of the Island of Cuba and established a military government. Of course, previous to that time sanitary records were very incomplete — not to say absolutely useless.

A survey showed that the mortality rate was taken up, to a rather considerable degree, by dysentery. As time passed it was observed that this record did not diminish to a great extent. The

water supply, at that time, was far superior to what it is today, because we then had the pure spring water, while now we are compelled occasionally, on account of the great increase in population, to let river water into our ordinary water-supply. Regarding dysentery, it became necessary to look around and find out the means of infection.

Those of you who have visited Havana may have observed, immediately in the suburbs, a large number of small truck gardens, probably one acre in extent, that are in the hands of Chinese. These people are in the habit of fertilizing their gardens in a very filthy and unsanitary way. We found that each one of these little gardens had a group of 8 or 10 Chinamen who lived together and took care of them. They had a big hole in the ground about 2 meters square, where they defecated, and into which they introduced swill and garbage obtained from Chinese restaurants, or wherever else they could get it. Having been warned by the authorities of the danger of this method of fertilization, late at night one of them would pick up a bucket of this mess and deposit on each lettuce plant a ladleful. The vegetables were very luxuriant and fine, and you can readily understand the amount of contamination produced in this way by such things when eaten raw.

A very active sanitary campaign took place, and this brought down the morbidity and mortality rate, which by that time we could appreciate because the records in the hospitals were being kept carefully. I thought this would be of interest to you.

Dr. Miguel Arango. — Allow me to give some information about amoebiasis in Barranquilla, Colombia, where I have practiced for many years. Amoebiasis in that city is very frequently encountered, although not so much now as it was in former times.

During 1915, dysentery ranked 4th as regards mortality, gastro-intestinal diseases of children, malaria, and measles having a higher rate of mortality. I must say that the mortality in the year 1915 was very great, after which measles decreased and disappeared, and dysentery ranked 3rd in the group of diseases. Then with improvement of the water-supply and more general use of septic tanks, dysentery showed a much lower mortality so that we may say it is not now very frequently found as an endemic disease at any rate, though it appears every now and then in mild epidemic outbreaks.

As regards the treatment of amoebiasis, I may say that we use, to a large extent, and with good results, the emetine, saline irrigations and arsphenamine. I have no experience as yet with the use of bismuth, which I expect, however, to use hereafter.

I may add that it is a long time since we have had amoebic hepatitis and liver abscess, and this coincides with the time in which we have used emetine. The last case was that of a patient with a history of dysentery, who came to Barranquilla from a town nearby.

Dr. Charles A. Kofoid. — For several years past it has been the custom at the Student Infirmary of the University of California to have stool examinations made in our laboratory in all cases of intestinal disorder, and in others of obscure nature. As a result of these examinations a number of instances of amoebiasis have been detected especially among patients returning from over-seas service or from foreign travel, as well as in those who have not been so exposed. After a series of tests by well-known methods of treatment for this disease (checked by stool examinations after the treatments) the method finally adopted by physicians in charge of patients has been the emetine-bismuth-iodide and emetine-hydrochloride treatment (recommended by the British Medical Research Council) but supplemented by neo-arsphenamine.

Owing to the severity of this treatment, it has been found advisable to carry the treatment only to the point of toleration. Treatment is suspended temporarily upon the rise of the pulse, and the patient is given digitalis.

In the epidemiology of amoebiasis, family infection is a striking feature. Our physicians have often found that when one case of infection has been detected in a family, examinations of other members will bring to light other infections. In fact, in some instances parents and children are alike infected, and clinical histories suggest an infection in a previous generation.

Not only in the university infirmary, but also among physicians using our laboratory service, there are many patients who report no previous history of dysentery or diarrhoea although a history of alternating constipation and diarrhoea is not infrequent. In a very large percentage of cases constipation is in fact a predominant intestinal symptom of chronic amoebiasis.

Patients reporting no previous history of dysentery constitute by far the greater proportion of instances in our records. However, it should be borne in mind that such testimony can hardly be expected to represent accurately the period of infancy and childhood within which amoebiasis may well have been acquired and may have been accompanied by an initial attack of dysentery, followed by the chronic carrier-stage, whose most evident intestinal characteristic is constipation. Indeed, to the student of comparative parasitology one of the most striking features noticed in the study of the infections of animals is the predominance of parasitic infections in the early stages of life. It is the young

animal which swarms with intestinal parasites. This is noticeably true in fishes and birds, and there is some evidence of it among the young of laboratory animals.

The diagnosis of amoebiasis is made by the microscopical examination of the stool. We employ a preliminary fresh smear in physiological salt solution and also in iodine-eosine stain, in order to detect the cysts of amoeba if they are present. We diagnose the presence of *Endamoeba dysenteriae* only on slides properly stained in iron haematoxylin. This stain makes it possible to differentiate with certainty the cysts of this pathogenic amoeba from yeasts, fungi, the cysts of flagellates and of other amoebae in the stool. It is our custom to call for 6 successive stools in making an examination; the basis of this is the fact that the number of cysts found in the stool in cases of infection runs an irregular rhythm of increase and decrease, with periods of apparently entire absence of cysts in the stool. Cases of infection examined by us over periods of several months, demonstrate the occurrence of these irregularities: 6 days is a sufficient interval to include one of the waves of increase as a rule. However, in some instances, examinations that extended over 30 to 40 days, with negative results, have been followed by a positive finding. In one case examined continuously by us in the Army Laboratory, New York, over a period of 46 days, the cysts were counted in a haemocytometer after stirring the entire stool to a uniform suspension with the Cyclone soda-mixer. The number of cysts varied in this period from none, in the sample examined, to over 800,000,000 per stool.

Physicians expert in the detection of the clinical signs of amoebiasis have often suggested that our examinations be continued beyond the routine of six consecutive stools meeting with success only in the detection of the infection in subsequent examinations. The use of a saline purge and keeping the specimen so obtained in a warm thermos bottle, is helpful in bringing to light the motile stages of the amoebae, — but to make an accurate diagnosis, one must rely upon the cysts. Recently we have been using with great success as a purgative a mild dose of bile salts during the period of stool-examination.

In his paper Dr. James has mentioned the occurrence of large and small amoebae found concurrently in the stool, interpreting them as phases of the life cycle. Permit me to suggest that these two extremes in size probably may represent a double infection of a large and of a small race. We find upon the transfer of human infection to culture rats, that the size of races of the amoebae transferred to the rat is maintained. Amoebae with large cysts continue to have large cysts, and *vice versa*. It is, however, not im-

probable that in the case of acute dysentery one will find in the stool the large motile amoebae feeding on red-blood corpuscles. These may attain diameters of 40 to 50 microns; and we may also find the smaller precystic stages. Prior to encystment, the feeding motile amoeba reduces its volume by the discharge of its food vacuoles, so that its diameter upon encystment rarely exceeds 15 or at the most, 20 microns. We might thus have in cases of acute dysentery both the huge, motile amoebae and the smaller precystic stages. Should these smaller stages diminish to diameters of less than 10 microns, one may suspect a double infection of 2 races.

We have no critical information as to the meaning of these *size races*. We do not know that they are genetic in origin. We do not know to what degree changing immunities during the course of an infection may bring about or be accompanied by changes in the dimensions of the infecting amoebae. The fact that many cases whose clinical histories indicate a long-standing infection, have so generally the smaller race of amoebae whose cysts may be only 4 to 6 microns in diameter, is strongly indicative of a possible modification in size as the result of long-continued contact with the host. On the other hand, cases of human infection continuously observed over a period of months, or at intervals during several years, and infections of human amoebae transferred to rats, — all these exhibit a continuity of dimensions of the cysts which clearly indicates that changes in dimension do not occur quickly. They can result only, if at all, from prolonged contact with the parasite and the host or under conditions at present unknown.

The cysts of amoebae remain viable for months, at laboratory temperatures, in water or diluted stools, but seem to die out in considerable numbers in unmodified stools. It is possible that many of them are killed by the process of fermentation. It may also be that the cysts are not all equally viable, — that there are only certain ones which are capable of establishing an infection in a new host. In the case of trypanosomes in the fly, it is well known that only a small percentage of infected flies become infective to man. Experiments upon cysts of amoebae made in my laboratory, by Dr. Bercovich of Hainan, China, suggest that not all cysts are equally permeable to disinfectants or to chemical reagents. We have found also that some cysts retain their normal stainability after weeks of drying, so that it may be that some cysts can be carried in the dust and remain infective, or at least viable over long periods. The prevalence of amoebiasis in semi-arid countries, such as Egypt, and on our own Mexican border, suggests that the fly — and possibly dust, as well as personal contacts — are the agencies in the dispersal of this infection among man. It is,

of course, possible that cysts may also be water-borne. However, they are of such a size and specific gravity that they will settle quickly in reservoir water, and will be much less liable to be water-borne than are the smaller and lighter bacteria. The agency of flies in the spread of this disease is strikingly illustrated by reduction in the amount of amoebic dysentery in Nanking, China, following two summers of an effective anti-fly campaign.

Dr. Lepine's data indicate clearly one of the sources of amoebic infection in temperate climates: namely, its exotic origin in persons returning from the Tropics. In our records compiled from the examination of 7,000 persons, we have many instances of the infection among those who have traveled in the Tropics and in the Orient, and of the spread of this infection to other members of the family. The individuals out of a group of 7,000, who reported traveling out of the State of California, — including those traveling in Europe, the Tropics and the Orient — were found to have over 100% higher infection by the entamoebae of amoebiasis than those not reporting such foreign excursions. Travel means multiplied personal contacts with contaminated food-handlers and other sources of infection. However, it would be quite a mistake to regard amoebiasis as restricted primarily to the Tropics. In our experience, it occurs among persons who have never traveled, and among those not exposed in any way — so far as can be determined — to tropical contacts. We have found it in Alaskan Indians and in persons from the remote rural districts of our State. The general impression that we derive from our statistics of occurrence among over 12,000 persons coming from many parts of the United States, is that amoebiasis is an age-old and race-wide infection of man, and that these infections are a result of the evolutionary process. Their geographical distribution is more a matter of sanitation, and of the means of communication, than it is of racial or geographical determination.

Dr. H. J. Nichols. — Dr. Kofoid referred to cultivation of the pathogenic amoeba, and I thought it might be of interest to make it a matter of record that at the June meeting of the American Society of Tropical Medicine, in Chicago, Dr. Boeck of Harvard University announced the cultivation of *Entamoeba histolytica*. If this reported event is confirmed, it may mean a very great advance in our knowledge of amoebic dysentery, because it has been tried for years and every one who has worked with amoebae has been anxious to know whether they have any enzymes and what the effect of drugs on them is. It would be much easier to determine this point with cultural amoebae, if they are available, than it is by making an examination of the stool, or by using non-pathogenic amoebae. It

is also possible, as Dr. Kofoid has said, that serological work may be done and both cultures and skin tests may become available. In other words, it may be an event, although it may remain a laboratory curiosity.

Sir Leonard Rogers has spoken of the history of emetine, and as a personal friend of Colonel Vedder I think a word is due to him, because he called attention to emetine under difficult conditions. He was working alone in a station laboratory, without any assistance particularly, with a large amount of routine work. He was in the Philippines and had great difficulty in getting the active principles of ipecac. He had only a few stray dogs to experiment with, but kept his main idea in mind and proved that the effectiveness of ipecac was due to emetine. He went only as far as to suggest that ipecac should be standardized for emetine. Sir Leonard Rogers made the important practical advance of using emetine alone. A word of praise is due to Colonel Vedder because it so often happens that the rewards of a scientific man's work go to the clinician and administrator, whereas the work is made possible by the personal work of the investigator.

In regard to the toxic effect of emetine, we feel that this is a definite thing, — and we have had several deaths in the Army from its effects on the myocardium. At autopsy, all that could be found was a thin cardiac wall; and speaking from personal experience I know that ⅔ grain taken over 1 week or 10 days can make a person feel as though he had locomotor ataxia. Speaking from personal experience, too, I also want to thank Dr. Deeks for bismuth subnitrate, which does more to stabilize the patient and relieve the "gone" feeling than anything else.

Dr. R. W. Hegner. — There are two points which were mentioned in the papers by Dr. James and Dr. Deeks that I should like to discuss. In the first place, Dr. James spoke a number of times of diet in cases of amebiasis. If I understood him correctly, he said that an excess of carbohydrates was advantageous for the development of the amebae.

Dr. W. M. James. — I said that in many of these cases which I treated the patients were on a faulty diet. I do not think this has anything to do with the amebic infection at all, but in after treatment of the case this diet must be corrected for obvious reasons, — not that it has anything to do with the infection.

Dr. R. W. Hegner. — I shall have occasion tomorrow to refer to the effects of changes in diet on certain intestinal protozoa. These experiments, however, do not include amebae, and I was interested in Dr. James' remarks because I thought he might have some evidence with respect to the effects of diet on amebae. Regarding

the distribution of amebae, Dr. Boeck in my laboratory did some work several years ago which indicates that the cysts of amebae live much longer in dilutions of feces than they do in raw feces, so that it seems they have a greater chance of reaching new hosts in a living condition when suspended in water, than when in undiluted feces. The ingestion of cysts with drinking water seems to me to be one of the main methods of the distribution of the cysts.

Dr. H. C. Clark. — The question has been raised about the frequency of negative reports on cysts in stools. Did you see them very often in the stools examined at Tela?

Dr. R. W. Hegner. — I saw very few cysts at Tela. There were a large number of amebae in cases that came into the hospital, but I was more interested in intestinal flagellates than in intestinal amebae during my stay in Tela, and so did not give the amebae much attention.

Dr. Charles A. Kofoid. — Permit me to direct the attention of clinicians to the fact that there is an amoeba of man, *Councilmania lafleuri*, which has clear pseudopodia, eats red-blood corpuscles, and has superficially a very marked resemblance to the motile forms of the amoebae of dysentery. It is, moreover, wholly resistant to all forms of emetine treatment; at least, it is not exterminated by such treatments. Its cysts have 8 nuclei, and thus resemble those of *E. coli*, but differ from them in the larger, subdivided, usually central karysome of the nucleus.

This amoeba often occurs coincidentally with the amoebae of dysentery, and persists after the extermination of the dysenteric infection. It might thus give a misleading picture of a failure to cure by the emetine treatment, unless one were on guard against such a misinterpretation. Its presence is invariably revealed by the occurrence of its characteristic cysts, although the motile stage is separated with difficulty from that of *Endamoeba dysenteriae*.

Dr. Seale Harris. — Dr. James spoke of the general difficulty of infecting animals with the *Entameba histolytica*. McCarrison fed *Entameba histolytica* to healthy monkeys and failed to infect any of them; but when he fed the organisms to monkeys that had been on an unbalanced high-carbohydrate and low-vitamin diet for a few weeks, it was easy to infect them with the *Entameba histolytica*.

Since Dr. Deeks' paper, or discussion on amebiasis, at the meeting of the Southern Medical Association, about 1910, I have been using large doses of bismuth subnitrate conjointly with emetine and the results have been excellent. We are seeing fewer cases of dysentery now than formerly, indeed, I think there is less dysentery in the South, owing to the marked improvement in sanitation in

the last one or two decades. I think one of the reasons why I personally see fewer cases is that the physicians in the country are treating and curing their cases of amebic dysentery by the use of emetin and large doses of bismuth. They do not wait to demonstrate the *Entameba histolytica* in the stools, but in any case of chronic or subacute diarrhoea they give emetine. I have never heard of any harmful effects resulting from emetine.

The diet which I use in these cases is low in carbohydrates and with a high vitamine content. I learned from the country practitioners in the South that an infusion of the green vegetables — particularly turnip greens and spinach — is helpful in dysentery. They claim that it is astringent, and that it cures the disease. I am inclined to the belief that the good effects of the green vegetables and "pot liquor," as it is called in the rural districts of the South, comes from the fact that it is a sterile diet and that it is not a good culture medium for bacteria or other organisms, and that it has a high vitamine content. I also use strained orange-juice and after a few days begin the milk diet.

Colonel Bailey K. Ashford.— Having seen little of amoebic dysentery in Porto Rico of recent years, I mention with some hesitation a case which I think should go before the Conference, of a man who came from Santo Domingo. I saw him in the afternoon and sent him immediately to the hospital, as he was suffering from an exceedingly bad dyspnoea. Before he got over to the hospital he was in such a bad condition that he became hopeless, and he died a few hours later.

I secured a short preliminary history of the case. He had had dysentery many years before, and had undoubtedly had what must have been liver abscess with perforation through the lung. Now he had no dysentery or diarrhoea, and all of his symptoms were from the chest. Dr. King, of the Public Health Service, and I spent the entire night on his autopsy. The right lung was completely atelectatic. The pleural cavity was filled with a clear fluid, and we at once noted an unusual thickness of the walls. When we came to examine the scraping from the pleural wall, we were simply astounded to see little more than a mass of amebae. There was no hint of pus or necrotic material. I only mention this as a rare and peculiar sequela of an old amebic dysentery from Santo Domingo.

With regard to the nutritional element in the treatment of these bowel diseases in the Tropics, I have nothing to add to Dr. Harris' remarks except to say that I am entirely in accord with him and that social-service clinics are being carried on in Porto Rico, as well as an educational campaign for better feeding.

Dr. A. R. Paterson. — It is with some trepidation that I enter into a clinical discussion, but I have had some experience with one of the drugs mentioned, *i.e.*, bismuth. Dr. Lepine has mentioned two arsenical preparations as being used in the treatment of amebic dysentery. Dr. James and Dr. Deeks mentioned bismuth as being very useful also in the treatment of dysentery. It happens that these arsenical preparations are exceedingly useful in the treatment of yaws if given intra-muscularly. In the treatment of yaws, bismuth is also exceedingly useful given intra-muscularly.

It is perhaps not generally known that while some salts of bismuth, if given by mouth, are exceedingly inert, others when given intra-muscularly may be exceedingly toxic. If you give more than 3 grains of bismuth sodium potassium tartrate intra-muscularly you may produce exceedingly severe stomatitis, so severe that it may even have a fatal termination. The point is this: — The situation of the ameba in the tissues of the intestine is not entirely unlike the tissue situation of the treponema in the granulomata in yaws. It would appear from the discussion that bismuth given by the mouth is useful in amebic dysentery, but another method may be suggested.

During the World War a preparation was used for the treatment of wounds and ulcers — called "bip" (B.I.P.) which contained bismuth, iodoform, and paraffin. In a number of cases, severe toxic symptoms resulted from the use of that preparation when it was used over a large area of broken skin, and the toxic symptoms were those of bismuth poisoning.

Dr. James mentioned, as one of the toxic symptoms of emetine, stomatitis. I do not know whether stomatitis has previously been recorded as a toxic effect of emetin, but I would suggest that the toxic symptoms in Dr. James' cases were not due to emetine, but were probably due to the absorption of bismuth from the ulcerated surfaces of the intestine. It is possible that the effect of bismuth salts given by the mouth is not due to the direct action of the salts upon the surface amebae in the intestine, but is due to the effect of the bismuth upon the amebae in the tissue and results from the absorption of a certain amount of bismuth through the ulcerated surface of the intestine.

There is this point that ought to be investigated because bismuth can be absorbed through the broken skin and can be very toxic. If you give it by mouth, and in large doses, and it is absorbed through the ulcerated intestine, then the dosage is entirely uncontrolled and one does not know how much may be absorbed. Small intra-muscular injections of bismuth in certain cases of amebic dysentery might therefore be a more useful treatment in

that disease, in addition to emetine, than large doses of bismuth given by mouth.

Dr. R. B. Nutter. — In treating amebic dysentery cases with massive doses of bismuth, we follow the practice of giving epsom salts about every 4th day to clean off the ulcers, remove the accumulated bismuth and give a fresh application. Although I know of no instance of intestinal obstruction from bismuth, the large firm masses of bismuth found at autopsy suggest the possibility of such an accident. I have never recognized symptoms of bismuth poisoning in dysentery, and doubt its occurrence.

The description of an emetine-resistant ameba is interesting, and I shall be able to demonstrate, to the members of the Conference who visit Tela, a patient who gives a history of recurrent dysentery for 20 years. I have treated this patient for 8 years, and, although the symptoms subside readily with emetine and bismuth treatment, the amebae are found in abundance — usually 2 months after the patient is discharged apparently well.

Bismuth emetine iodide, 30 grains in 10 days, has proved very satisfactory in some resistant cases, but it is unsatisfactory as a routine treatment in hospital, as in many instances it provokes vomiting.

We use the bismuth-emetine treatment as described by Dr. Deeks. Mortality occurs only in patients who are admitted moribund and hepatic; abscesses are very rare.

Dr. E. Urueta. — The treatment for amebic dysentery — outlined by Dr. James — with bismuth-emetine is the best method of treatment used in Santa Marta, Colombia, where the disease is endemic. This treatment is carried on while the patient is in the hospital. When he leaves some bismuth is given to him, to be taken according to instructions. While the patient is in the hospital he stands the bismuth very well, but as soon as he leaves and resumes his ordinary diet, constipation ensues, with all its inconvenience, which makes the patient stop the treatment.

To overcome this inconvenience I have tried with very good results small doses of ipecac powder in a gelatin capsule, at bedtime. We give it at this time to avoid the nauseating effect of the drug. The dose may be from 3 to 5 grains, according to the tolerance of the individual. An adult can easily stand a dose of 5 grains. The stimulating action of the ipecac on the liver functions — in increasing the amount of the bile and other intestinal secretions — combined with the stimulating peristalsis of the bowels, prevents the bismuth from forming compact masses and retention — thus avoiding the alteration of the bismuth which may liberate the nitrates contained in the bismuth salt that may cause poisoning.

I have had the experience of several relapsing cases, despite the regular emetine and bismuth treatment for various periods, which have been definitely cured by the bismuth and ipecac treatment.

Dr. A. A. Facio. — Regarding the interesting point brought to our attention by Dr. Paterson in alluding to bismuth poisoning, I would like to mention a case of neuritis of the nerves of the left arm produced by the excessive ingestion of bismuth.

The patient referred to, who came to our hospital in Port Limon just a few weeks preceding our departure, had been taking on an average ½ pound of bismuth a month. We thought at first that it was an ordinary case of neuritis produced by anything else but bismuth, but, as it did not respond to the treatment instituted, we suspected that the trouble was possibly caused by the enormous quantity of bismuth the patient had been taking. An examination of the blood was made, and the blood-picture was in general very much like that seen in cases of lead poisoning.

This case was treated by intravenous injections of sodium iodide, with a view to obtaining bismuth iodide, which, unlike the bismuth salts, is soluble, and thus possible of elimination — 6 injections were given at an interval of every 3 days, at the end of which period all the symptoms had disappeared and the patient fully recovered.

It was of interest to observe that when the sodium iodide had been injected into the veins of the *opposite* arm, the *affected* arm swelled to about double its natural size, although the swelling subsided each time after a few minutes.

Dr. William M. James (*Closing the Discussion of His Own Paper*). — I was very pleased to hear Dr. Lepine's statement as to the etiology of the amebiasis which he found in France. Like others who have discussed this paper, I believe that the evidence points strongly to a contact infection, and this view is borne out by the reports of several of the French observers at the front where the French Colonial troops were confined in the trenches for several days at a time.

One very able writer, Dr. Jaques Carles, wrote a monograph on dysentery, in which he showed how some very interesting local epidemics of amebic dysentery were confined to trenches, in which 2 or 3 of the Colonial soldiers had been mixed up with, say, a dozen or more French soldiers who had not left France, — and under those conditions the soldiers who had not been exposed came down in large percentages in these restricted areas.

As to whether water supply transmits amebic dysentery — that is a question to be determined by experimentation and work. It has always seemed to me that it is an unreasonable method of transmitting the cysts, even granting that they are viable in water, be-

cause it would take so many cysts to infect a large supply of water, and the law of averages and chance is against infection in this manner. However, I am entirely open to conviction.

Now, with respect to Dr. Kofoid's well-taken point about not confusing the life cycles of the different strains of the amebae found in the stools, perhaps I did not make myself clear on that point, as I condensed my paper. What I meant was, that I do not think a species should be established solely on what is found in the stools. I think we should look further, in the higher part of the large intestine, to find if there is one common type of ameba which is in its normal home there, and appears in the stool as small amebas of varying sizes. We have had frequent occasions to test this, as we have patients who have a chronic type of amebiasis and in whose stools small amebas will be found. When we look in the appendix we find the ordinary large vegetative form, which is classed as *Entameba histolytica*. I think the protozoölogist, in building up his species, should take this into account, and not determine species only on what he finds solely in the stool.

In regard to Dr. Connor's point — I am afraid I did not make myself clear there. What I meant is this: — We encounter a combination of amebic infection with other troubles which cannot always be traced to amebas. The appendix, gall bladder, uterus, — a vast variety of organs — present other conditions for which our patients come to see Dr. Runyan and Dr. Herrick. These patients frequently have also amebiasis. In order to save time we used first to treat the patients with emetine and bismuth, and afterward operate.

The results in some of those cases were very disastrous, so much so that neither Dr. Herrick nor Dr. Runyan will touch any more surgical cases (unless it is absolutely necessary) in which emetine has been previously given in large doses until the danger period is passed. If I were in the presence of an acute amebic abscess of the liver, I would give emetine, but I would watch the effect very carefully — and my two surgical colleagues do not like to give it even then, prior to operation, unless the need for this is urgent. We have had some personal experiences, in which lessons taught us have made us very cautious in operating on emetine-filled patients.

I am aware that I give larger doses of emetine than do most physicians. My reason for that is — and I may be wrong — if a little emetine will do some good, more ought to do more good. When a clinician of Sir Leonard Rogers' vast experience states that in a large number of his cases — many thousands more than I have ever seen — when emetine only is used he has a good many relapses — then I think I might use more emetine than is generally advised.

Mine is not a method of treatment which I recommend at all in general practice. I do not use it unless I can administer it myself, or have well-trained nurses do it for me. I have no doubt whatever that there are other methods of treatment which give good results, and that time will bring us still other treatments which also will give us excellent results.

After all, the problem is to get rid of the entamoebas. We must get rid of the entamoebas in the intestinal lumen, as well as in the tissues. If we can get rid of the entamoebas in the lumen, very often nature and time will take care of those in the tissues. This must be so, because undoubted cures have been brought about by irrigations and other systems of treatment which are more or less mechanical, and which could not possibly have affected the entamoebas in the tissues — but they did get rid of the entamoebas in the lumen of the bowel, and then the tissues took care of their own entamoebas.

This must be true for no one who has seen the pathology of amoebic infection, and then considers how many cases go along without any treatment at all — relapsing today being a little better now, a little worse tomorrow, going on for years in this manner — no one who has observed this can fail to see that there is some ability on the part of the tissues themselves to handle the entamoebas in them.

In regard to what Dr. Paterson asked about stomatitis — of course I cannot say that stomatitis was not brought about by bismuth, because bismuth and emetine were both given at the same time. I stopped the emetine and continued the bismuth, and the stomatitis cleared up.

I wish to congratulate Dr. Lepine on his excellent presentation of his subject.

Dr. Pierre R. Lepine (*Closing the Discussion of His Own Paper*). — First I shall answer the remarks of Sir Leonard Rogers, in regard to the use of Stovarsol, alone, without emetine, in the treatment of amoebiasis.

As a matter of fact, we generally use emetine alone, but may combine it with Stovarsol or Acetylarsan. We began to use Stovarsol alone, to try to recognize the efficiency of the drug, and it was found at that time so efficient and so easy to give by mouth — and without even modification of the diet — that we now give treatment with Stovarsol alone to patients in private practice, and to those who cannot come often to the hospital.

Next, in reply to Dr. Paterson's remarks as to the toxic effects of the drugs: It would take too long to give you the results of experiments with Stovarsol and Acetylarsan on rabbits and guinea-

pigs, but these tests show that the curative dose given to man is far below the toxic doses of the drugs; and I must repeat here that we have not observed any bad toxic effects which could be traced to the drugs.

In closing this discussion, I should like to draw your attention to another point raised by Sir Leonard Rogers and Dr. James, *viz.*, how rare dysenteric symptoms are in our patients: —

Most of them have only chronic diarrhoea. Many were treated before coming to us for intestinal tuberculosis. Some patients had not even diarrhoea. I remember a case of a young woman who had no dysentery, and not even diarrhoea. She suffered only from abdominal pains in her right side. She came to the surgeon thinking that she had appendicitis. During the course of the examination, the surgeon noticed that the whites of her eyes were yellowish, and on inquiry found that she came from Indo-China. He asked her if she had had dysentery in Indo-China; she said not, but that her husband had had it. The surgeon, who proved to be a very clever man, asked for an examination of feces, which was made. The stools were normal in appearance, only a little shiny on the outside, but abnormal in that they were full of cysts. Treatment was given with emetine, and the patient was cured without any operation.

Such cases ought to be known, because these patients are unknown carriers of amoebae and, from this point of view, play an important role in the etiology and epidemiology of amoebiasis.

Professor P. Mühlens. — In the discussion of the treatment of amoebic dysentery, in which I could not take part, because of my late arrival at the Conference, Professor Fülleborn was asked by Dr. Connor to give some data on the Yatren-treatment of this disease. Professor Fülleborn reserved the answer for me.

We all know that the introduction of the emetin injections in the treatment of amoebic dysentery must be considered as one of the most important steps of progress in tropical therapeutics. But we do not know, as yet, any one specific medicament which cures every case of the corresponding disease with absolute certainty. Thus, we have all seen cases of amoebic dysentery, especially the chronic form, which, in spite of intensive emetine treatment, did not definitely heal, but which recurred again and again for years and years. This experience caused many doctors in the Tropics to search for other medicaments or adjuvants for this purpose. So also we.

Two cases which resisted for a long time every form of treatment, including appendicostomy or coecostomy followed by irrigations, led Dr. Menk and me in the Hamburg Tropical Institute to treat these cases with Yatren irrigations of the intestines through the operation fistula. Both cases were cured in a few weeks.

After vain trials with irrigations containing silver nitrate, tannin, quinine, and even iodin solutions, we were driven to the Yatren treatment, especially because surgeons had claimed for it a highly penetrating antiseptic effect. According to the reports of the Behring-Werke (Marburg), Yatren is an odorless iodoöxyquinolin-sulphuric-acid combination in which the iodin is firmly bound. The Yatren is easily soluble in warm water, and easily tolerated when given in pills or in powder form by mouth; it is also given by enema in a 2% solution. *Dose:* 3 to 4 times daily 1 gram (about 15 grains) for 1 week; or 1 enema daily of 200 cc. of a 2% Yatren solution introduced after cleaning out the bowel by means of a copious clyster.

The fluid — and this is important for the results — must be retained as long as possible. Most of the patients finally succeed in retaining and absorbing the injection. After these first treatments for 1 week, it is useful to repeat the treatment on 2 or 3 days during the 2 following weeks. In the Hamburg Tropical Institute and in the Tropical Sanatory Tubrugen, the Yatren treatment has been given for 4 years with good results.

We used the local rectal application of Yatren, especially in resistant chronic cases with local ulcerative lesions visible by proctoscopic inspection, with the very best results. The amoebae, and in most cases also the cysts, disappeared in a few days, the stools became normal, and the ulcerations healed within 1 to 2 weeks. But also by the pills and powder treatment by mouth, as mentioned above, we and many other observers had very good results.

Today I cannot enter into the details of the results published by many authors of many institutes in many parts of the world. I will mention only the cures obtained in the Dutch Tropical Institute (in Amsterdam) by Kuenen; in Rio de Janeiro, by Silva Uello; in the Institute Bacteriologico, Buenos Aires, by Sordelli; and in Brussels, by Broden. Further favorable reports have been obtained and published by many Dutch doctors of Java and Sumatra, in Brazil, China, Japan, and Central and South America.

Since my first communication, in 1921, I have been anxiously waiting for the results obtained in different tropical countries. Now, in consequence of the very numerous favorable experiences in chronic, and also in acute amoebic dysentery reported by others from many parts of the world, I think I can with the best conscience recommend this treatment, especially in all resistant chronic cases, as an undoubted step forward in the treatment of amoebic dysentery, in addition to the classic emetine treatment with which the name of Sir Leonard Rogers will forever be associated.

SURGICAL COMPLICATIONS AND TREATMENT OF INTESTINAL AMEBIASIS

R. W. Runyan, M.D. and
A. B. Herrick, M.D.

The complications requiring surgical intervention during the course of, or following, amebic infection of the intestines, naturally divide themselves into two distinct groups: i.e., those arising from the direct action of the parasites; and those of purely mechanical origin, the result of severe diarrhea and tenesmus.

The latter group will be only briefly mentioned, as they are in no way distinctive, in either symptoms or treatment, from similar conditions arising from any other severe diarrhea. Under this head, we find pruritis ani, anal fissures, internal and external hemorrhoids, and varying degrees of rectal prolapse. Occasionally, some of these conditions may require treatment during the course of the disease, but such treatment is preferably postponed until the infection is either cured or under control. The introduction of emetin in the treatment of amebiasis has markedly reduced the number of complications of all types; for it controls the severe diarrhea and, by shortening the duration of the acute symptoms, prevents the occurrence of many of them.

It is with the group of complications caused by the direct action of the amebæ that we are chiefly concerned, and these we will discuss in some detail, limiting ourselves, however, to our personal experience with these conditions.

As the large intestine is the natural habitat of the invading parasite, it may reasonably be supposed that it would more often be affected with surgical lesions than other parts; and if the appendix be included as a part of the large bowel, this is true, judging from the cases that we see. By far the large majority of cases of amebic infection that we see,

at the present time, are those of the so-called latent or carrier type. These patients have had an acute attack of dysentery, have been treated by emetin and not cured, or have had an infection that has remained more or less quiescent, unrecognized, and of course, untreated. A majority of such patients will present distinct localizing symptoms in the region of the appendix. The symptoms vary, from mere discomfort in this region, up to typical attacks of appendicular colic; and in two instances we have seen localized appendix abscesses, apparently due to amebæ.

On examination, we find more or less tenderness over McBurney's point, possibly some muscle spasm, and frequently what seems to be a thickening of the cecum. These findings, combined with a history of indigestion and possibly alternating attacks of constipation and diarrhea, are so characteristic of this type of case, that many times a tentative diagnosis of chronic appendicitis and intestinal amebiasis can be made before looking for amebæ in the stool.

Before we learned to recognize this symptom complex, many of these cases were operated upon for chronic appendicitis, and a chronic appendix and numerous adhesions were found; but the thickening of the bowel, or the occurrence of a diarrhea during convalescence, would give us a clue to the etiology, and search of the stools would reveal amebæ many times after repeated negative examinations. After we had these experiences, the pendulum swung back the other way. We became ultra-conservative in the treatment of these cases of apparent chronic appendicitis co-existing with amebic infection, and depended upon medical treatment for a cure. In this we were disappointed,— in almost all instances we failed to obtain relief from the local symptoms, and in many of them reflex indigestion or chronic appendicitis persisted.

It also seemed that some of our failures to cure the amebic infection might have been due to re-infection from the appendix. This possibility led us to believe that the proper thing to do would be to remove the appendix and release the adhesions, only after thorough and apparently successful treatment of the amebic infection had failed to relieve the local symptoms.

While the ultimate results following this line of treatment were almost uniformly good, yet, it seemed that our operative patients did not do as well as the ordinary cases of chronic appendicitis. Convalescence was prolonged; meteorism and abdominal distress following operation were more marked; wound-healing was not as prompt nor as good; and we finally came to the conclusion that optional surgical intervention immediately following the routine treatment of intestinal amebiasis was not advisable. We feel that these undesirable symptoms following operation were due to the effects of the emetin used in the routine medical treatment. Moreover, since most of our patients come to us from a considerable distance — and therefore cannot return for operation at some later date — we have gradually evolved the following routine:

All cases of apparently definite chronic appendicitis, with co-existing latent intestinal amebiasis, are advised to have an appendectomy performed, to be followed in about 10 days by the routine medical treatment. The operation which we prefer and always use if there is no other surgical indication, is, the muscle-split, or so-called gridiron operation of McBurney. Should this not provide sufficient room for the necessary manipulation, additional space can be secured by means of a transverse incision across the outer border of the right rectus sheath, and a retraction of the muscle toward the mid-line. The cecum is brought up, and any adhesions of it and the terminal ileum are released; the appendix is separated from the meso-appendix, ligated, cauterized, and inverted by purse-string suture. The abdominal wall is closed in layers.

These patients will usually be feeling fairly well by the 3rd day, are allowed to get out of bed as soon as they desire to, and usually by the 4th or 5th day they are up in a chair or walking around. Stitches are removed about from the 7th to the 10th day, and after this the treatment of their infection is begun.

We feel certain that our results are better following this routine than they were previously, and that there is less liability to relapse after the removal of a reservoir such as the chronically inflamed appendix, often harboring amebæ in its contents.

It is worthy of mention that among the many patients of this type that we have seen, none of them developed symptoms of hepatitis, or liver abscess, even though in some instances a positive diagnosis could not be made for some time after the patients were seen.

We have mentioned that we have seen two cases of acute appendicitis with abscess formation apparently due to amebiasis. In one of these the appendix was removed and the abscess was drained; then, after appropriate treatment of amebic infection, the patient made an uneventful recovery. In the second case, it was deemed inadvisable to remove the appendix, because of difficulties encountered at the time of operation, and therefore the abscess cavity was simply drained. Unfortunately, the etiological factor in this case was unknown, the abscess continued to suppurate, and several weeks following operation a suppurating sinus developed at the umbilicus. Both the abscess cavity and the umbilical sinus continued to suppurate, and the patient finally died from exhaustion. The autopsy revealed that he had had a general peritoneal amebic infection; and that the suppurating sinus at the umbilicus was in extension, by way of the round ligament from the general peritoneal infection; in all probability the appendix abscess was from the same cause. In addition, this patient had a wide-spread infection of the meninges with amebæ.

Among the conditions affecting the cecum, we want to call your attention to a rare condition of which we have seen 4 cases, but which, so far as we know, is undescribed in the voluminous literature on amebic dysentery,— unless the amebic tumors of the large intestine, described by Lasnier[1] refer to this condition. We have been unable to see Lasnier's original article and have seen it mentioned only in a brief abstract. The rare condition referred to is the massive type of ulceration due to chronic amebic infection, causing enormous thickening of the wall of the bowel, a condition which, in turn, affects not only the cecum but also the terminal ileum:—

The first case of this type that we saw was thought to be a tumor of the kidney, because of the presence of a freely

[1] "*Anales de la Facultad de Medicina,*" *Montevideo.* Nov. and Dec., 1918, 3, No. 11-12.

movable large tumor without any history or symptoms pointing to an intestinal condition.

The second case was thought to be a cancer of the cecum, on account of the history of obstinate attacks of constipation, amounting almost to absolute obstruction and followed by attacks of diarrhea. The patient was thin, anemic, and in generally poor condition, having the cachectic appearance that one instinctively associates with malignant disease.

The last two cases were correctly diagnosed, by reason of our previous experience; amebæ were found in the stool previous to operation,— after repeated negative examinations in one case.

All of these cases were operated upon, and in each instance it was found necessary, because of almost complete obstruction of the bowel, to excise the cecum, part of the ascending colon, and a portion of the terminal ileum. After the excision, an end-to-side anastomosis of ileum into ascending colon was made. Of these patients, 3 out of 4 recovered; the 4th died from shock following operation.

Because of the generally poor condition of patients of this type — run down and anemic as a result of their chronic infection and long-standing impairment of bowel function — the operation required is a very serious one, but we do not believe that it can be evaded. For, judging from the appearance of the excised specimens in these cases, it would seem that it would be impossible to effect a cure in any other manner.

In this connection, we should like to call your attention to the fact that, while it is repeatedly stated in text-books that the amebæ do not infect the small bowel, and that the lesions due to them are always in the large intestine, yet here are four cases in which the small bowel was also affected, nor did one of them fail to show large ulceration and induration of the terminal ileum. This involvement of the small intestine is very probably an extension of the process from the cecum, due to the almost complete obstruction and the consequent damming up of intestinal contents.

Another uncommon condition in our experience is the intestinal hemorrhage. Bleeding of any severity from the bowel, except during the acute stage of dysentery, has been

seen but a few times. In a recent case, a woman of about 50 years of age, had fissured, ulcerated hemorrhoids, and after several futile searches for amebæ had been made, it was thought that the bleeding came from the hemorrhoids. Excision of the hemorrhoids was effected, but the bleeding persisted, and on proctoscopic examination it was noted that the blood, although fairly bright red in color, came from above the rectum. It was then thought probable that we were dealing with a case of cirrhosis of the liver. But, after several negative examinations of the stool, amebæ were found, and the administration of emetin and bismuth brought prompt cessation of the bleeding.

Extremely rare during recent years, but very common previous to the introduction of the modern treatment of intestinal amebiasis, have been the cases with very severe colitis. These patients were usually in very grave condition, having 20 to 30 bloody stools daily, and were as nearly dehydrated as a living person could be,— emaciated until they were nothing but skin and bones. Such cases we treated with continual irrigations of the large bowel following appendicostomy, or, more frequently, cecostomy. The operation could be performed under local anæsthesia, the appendix or cecum being pulled up through a muscle-split incision, a rubber tube sewed in, and an irrigation being started immediately. The operation itself was trivial, adding nothing to the risk incurred by the patient, and a large percentage of cases so treated were very successful; so much so, that even apparently moribund cases were occasionally saved, and subsequently cured. Among other conditions affecting the large bowel we have seen ulcerations of the rectum which have only rarely required any surgical treatment. However, in several instances a diagnosis of amebiasis could be made from smears taken from these ulcers, when ordinary stool examinations had proved negative.

Of the complications outside the intestinal tract, abscess of the liver is by far the most important. The symptoms of hepatic abscess vary so greatly, according to whether they are of the acute or chronic type, that we prefer to describe them separately:—

The acute abscess or abscesses — for they are sometimes

multiple — usually will arise during the course of, or following, an acute attack of dysentery, although they may develop in a case of the latent type of amebic infection. There are generally a rise in temperature, chills, and sweats, and pain over the liver. Pain in the shoulder, on the affected side, is a very common symptom. The nearer the abscess is located to the superior surface of the liver, the more marked will be the local symptoms, and it is in cases of this kind that we find symptoms and signs of diaphragmatic pleurisy.

On examination, it will be found that there is some restriction of respiratory movements on the affected side, and there may be some localized bulging of the thoracic wall. The liver will be found to be enlarged, and, as most abscesses occur in the vault of the right lobe, the enlargement will be found to be most often upward, extending from the nipple line, in front, around to the posterior axillary line. Usually some spasm of the abdominal muscles will be noted on the affected side, and there is marked tenderness, upon percussion, over the liver.

In a case of this type there may be signs of compression of the lower part of the right lung, with impaired resonance and fine crackles over the diaphragm. There is an increase in the leucocyte count, especially of the polymorphonuclears, as well as anemia of varying degrees. Previously, in only about one-half of the total number of cases was it possible to find amebæ in the stool; but since we have learned to recognize the small forms of the parasite, it has been possible to find them in almost every case, although occasionally only after repeated negative examinations. In cases in which the diagnosis is doubtful, X-ray will be found to be of service.

There are also cases in which there is a shower of multiple small abscesses affecting all parts of the liver. This is apparently a terminal condition, and, in our experience, has always proved fatal.

The abscesses of the chronic type are insidious in their onset, and are most often afebrile, or nearly so. There is no marked change in the white-blood count, and the pain and tenderness are not as pronounced as in the acute cases. It is in this group that the largest abscesses are found, and

often the enlargement of the liver will be enormous, although occasionally a fairly good-sized abscess of central origin will be present, with very little evident enlargement of the liver.

The abscess may be pointing toward the surface, or may have ruptured externally or through the lung before the patient has been seen by the surgeon. If it has ruptured into the lung, there will be a cough and expectoration of typical liver-abscess pus. The general condition of these patients is very poor; they are anemic, emaciated, and usually very weak, the general debility being much more marked than in more acute cases.

The treatment of a condition as varied in its symptoms and pathology as liver abscess, obviously cannot be on the basis of any hard-and-fast routine. In the large chronic abscesses pointing externally, or with well-defined localizing signs, it has been our practice to perform a simple incision and insert a drainage tube, under local anæsthesia; we have found that this answers the purpose as well as more elaborate procedure. These abscesses are practically always solitary, and until just recently we had never seen a case of this type requiring a secondary operation, for a second abscess.

Lately it has been recommended that abscesses be aspirated, repeatedly if necessary, and emetin injections used in treatment. Judging from the cases reported as cured by this method, they seem to fall into the category of chronic abscesses.

We have had no experience with this method of treatment, but cannot see that it offers any improvement over simple incision and drainage,— especially for those cases that can be treated under local anæsthesia, as there is always the probability of repeated aspiration being necessary, and occasionally the possibility of more radical surgical measures. For this reason, we would hesitate to abandon the simple operation, which is no more painful than aspiration, and does not require repetition.

In the more centrally located chronic abscesses, and in practically all acute cases, without definite localizing symptoms, it has been our custom to make a small right-rectus exploratory incision, just enough large so that the hand

may be introduced, and the liver palpated for the localization of the abscess or abscesses. After the abscess is located, drainage is obtained in whichever locality it can best be established. This may require a secondary abdominal or thoracic incision. If an abdominal incision is necessary, it is made small — just large enough to admit an adequate-sized drainage tube and a few strips of iodoform gauze to wall off the general peritoneal cavity.

If the abscess is in the vault of the right lobe, rib resection will be required; and if it is sufficiently high up, suture of the pleura to the diaphragm will be needed, to prevent pneumothorax or empyema. We make no effort to anchor the liver to either abdominal or costal wall. Abscesses are opened immediately, first a large aspirating needle being used, and then a blunt forceps. The drainage tube is inserted and the area packed off as well as possible by multiple strips of iodoform gauze.

Pus is evacuated by posture or suction, but no irrigations of any kind are used, neither do we wipe out or pack the abscess cavity with gauze, as we feel that to do so might open up new channels through which the causative organism might be carried beyond the liver. The gauze drains are either partially or completely removed by the third day, and the drainage tube is shortened, or replaced by a smaller one, very gradually. The abscess cavity gradually contracts and the external sinus closes, the time required depending largely on the size of the abscess and the condition of the patient. We, of course, give these patients emetin and bismuth; but the former must be administered very carefully, as many of these patients are profoundly prostrated, and do not take the drug well.

Our mortality following this line of treatment has been but 5%. However, abscesses are so uncommon that we have had but 21 in the past 6 years, and it was the last of this series that died.

We prefer an abdominal exploratory incision in these acute cases, for several reasons, chief of which is the certainty of definitely locating small or centrally situated abscesses, which might easily be overlooked if one depended on aspiration solely. Such an incision also partially obviates the possibility of overlooking a second abscess in

the *other* lobe of the liver. In several cases, we have found more than one abscess, and at least half of them were not suspected previous to operation. We also feel that the actual opening and the drainage of an abscess can be more advantageously located if this method is used. In addition, our results have been so uniformly good, following this procedure, that we would hesitate to change our routine for other methods which apparently offer no special advantages.

Among the rare complications, we have seen two cases of amebic abscess of the brain, both of which were very rapidly fatal. One of these cases followed the opening of a large acute abscess, in which the cavity was mopped out very thoroughly with gauze. The other occurred in a case in which, after a long period of drainage, we curetted a small sinus, probably an inch or an inch and a half in depth, which showed no tendency to close. Upon these occasions, symptoms of meningeal irritation promptly appeared, and in both instances the patient died within 48 hours. The rapid appearance of meningeal symptoms in these 2 cases led us to believe that it was very probable that the traumatism of the abscess wall permitted the extension of the infection. Accordingly we altered our operative technic so as to cause the least possible injury of this kind.

Amebæ will occasionally destroy large sections of the abdominal or the thoracic wall. We have seen 2 cases of this type follow cecostomy, one of them after a trans-thoracic opening of an hepatic abscess. However, these cases, as well as the 2 cases of abscess of the brain, previously mentioned, were seen previous to the introduction of emetin in the treatment of amebiasis, and probably no such case would ever occur when this drug has been properly used.

THE PREVENTION AND TREATMENT OF AMOEBIC HEPATITIS AND LIVER-ABSCESS

LEONARD ROGERS, F.R.C.P.

During the last two decades advances in our knowledge of the etiology, prevention and cure of amœbic liver abscess have been made which have scarcely been surpassed by those of any other branch of tropical medicine. A brief outline of this I desire to bring before you, based mainly on my twenty years' researches on the subject in Calcutta, where I commenced work as a pathologist in 1900. Then amœbic dysentery had not even been discovered in India, and was not recognized as a separate entity by such an authority as the late Sir Patrick Manson until several years later — although Kartulis had described it in Egypt in 1883, and Councilman and Lafleur in the United States in 1891.

Moreover, in spite of Kartulis' having discovered amœbæ in liver abscesses in Egypt, in 1887, there was still much difference of opinion as to its etiological value, for it had been found in less than half the few recorded cases in which it had been looked for, while a very brief study of the literature of that time, when Shiga had only just discovered his organism of bacillary dysentery, suffices to show the hopeless confusion regarding the classification of dysenteries, and still more of the relationship between them and tropical liver-abscess. Dr. Andrew Duncan, as late as July, 1902, in opening a discussion of dysentery at the British Medical Association, took the line that single large tropical liver-abscess was not related to dysentery at all, although he candidly acknowledged to me a year later that my paper, read immediately after his address, upset nearly everything he had said on the subject, and in that communication I recorded the following results of my first two years' work in Calcutta:—

I first showed that amœbic dysentery, so far from being unknown in India, was in fact quite common in Calcutta;

that large tropical liver-abscesses occurred only secondarily to amœbic dysentery, and never in the bacillary form; but they occurred most frequently in latent forms of amœbic bowel-disease, with a slight ulceration limited to the cæcum and ascending colon, as illustrated by the diagram I show you of the post-mortem appearances in nearly 100 cases. Further, by examining microscopical scrapings from the walls of liver-abscesses, post-mortem or at the time of opening, I was able to show the presence of living amœbæ at the active seat of the disease in every case, while bacteriological examinations proved that over 80 per cent of them were sterile on culture, proving that the amœba was the only common and constant cause of the suppuration. The frequency of the association of liver-abscess with dysentery, which Duncan then denied, was investigated in a series of 63 cases, in which both clinical notes and post-mortem records were available, and revealed 55.5 per cent with both forms of evidence, 20.63 per cent with post-mortem, but no clinical evidence, and 14.3 per cent with only clinical, but no post-mortem evidence; no less than 90.48 per cent being thus positive; while some years later my own post-mortems showed 98 per cent of 50 cases positive: the dysentery always being of the amœbic variety.

I have recalled this old work only because it was the foundation of my many years' labours to place the treatment of amœbic hepatitis on a firm scientific and successful basis, for, at the time I have been speaking of, the old empirical methods of those great Anglo-Indian doctors, McLean and Norman Chevers, of preventing the development of tropical liver-abscess by the treatment of the earlier stages of tropical hepatitis by ipecacuanha, had been largely forgotten, as is easily proved by the fact that a search through the whole of the records of the large European Calcutta Hospital for three years at this period showed that in no single case, of scores of hepatitis and liver-abscess, had ipecacuanha been given, ammonium chloride having replaced it with most unfortunate results, as shown by the temperature charts I show you of liver-abscesses developing after four weeks treatment by the later drug in the hospital, with fatal results.

The proof that tropical liver-abscess, as it had hitherto

been called, was in fact due to an amœba, and was nearly always free from pyogenic organisms, at once opened the very important question whether the invariable custom, at that date, of opening and draining such abscesses was necessary or the best and safest procedure; for the mortality following the open operation in the British Army in India was between 50 and 60 per cent, while in the more advanced cases coming to civil hospitals it was as high as 70 per cent, clearly leaving room for improvement. Moreover, I had been making cultures, at the time of dressings, in a number of cases in which the pus, aspirated into a sterile test-tube immediately before the abscess was opened, had proved free from cocci and bacteria, and I found that in the damp, germ-laden Calcutta climate no case was ever sterile three days after opening, with the inevitable sucking in and out of air at every respiration during the frequently required dressings. And later, Major G. C. Spencer, R.A.M.C., while Professor of Surgery at the Royal Army Medical College, candidly recorded his opinion that such secondary septic infection after the open operation on large liver-abscesses is quite unavoidable, and is indeed the cause of the high mortality following the procedure.

As early as 1902, I found by experiment on fresh post-mortem liver abscesses both that quinine bihydrochloride in a strength of 1 in 100 rapidly rendered the living amœbæ immobile, and that their protoplasm became granular; and I advocated aspiration and injection of quinine into the liver-abscess cavities after removing as much pus as possible, in place of the open operation, much in the same way that tuberculous abscesses are aspirated and injected with such substances as iodoform. But it was several years before I could persuade a surgeon to try my plan, and in the meantime I had made a still more important advance, which I must next relate.

REDISCOVERY OF THE VALUE OF IPECACUANHA IN AMŒBIC HEPATITIS

Having discovered amœbic dysentery to be so common in India, where ipecacuanha had so long held a high reputation in dysenteries in general, I naturally tried the drug in amœbic disease, although, curiously enough, Councilman

and Lafleur, in their classical description of amœbic disease of the bowel, had recorded the failure of ipecacuanha in its treatment. And I very soon came to the conclusion that this drug was indeed active in amœbic, but not in bacillary dysentery, although Manson had not then differentiated the two forms of dysentery, or their treatment, in his classical book on tropical diseases. I had also been making blood-examinations in long-continued fevers in the European hospital, for some years, with a view to their differentiation, and noted that some obscure fevers, with no very definite clinical features, occasionally developed liver-abscess after several weeks in the hospital. I observed too, that leucocytosis might be present long before any signs of suppuration were evident, and that in the more chronic cases the proportion of polynuclears was either only slightly, or not at all, increased, as is the case in ordinary septic inflammatory conditions, and I designated this early stage as *presuppurative amœbic hepatitis.*

In such cases there were very rarely any dysenteric symptoms while patients were in the hospital, and in some of them no history of previous dysentery was obtainable, but if such patients died (after the opening of the liver abscess) a few small amœbic ulcers were almost invariably found in the highest part of the large bowel, being the primary focus from which the liver abscess arose. It was while on the lookout for early cases of liver abscess, to try to get my plan of aspiration and injection of amœba-destroying drugs into the cavity, tested, that I met with a number of such cases; and in 1905 I recorded blood-counts in hepatitis and liver-abscess cases, showing that 10 cases with a leucocytosis of upwards of 12,000, and 1 with a relative leucocytosis (red 2,860,000 and white 8,625) went on to liver-abscess formation under treatment by ammonium chloride, which I had never seen do the slightest good in tropical hepatitis. I also recorded, in this paper, my first case in which acute hepatitis with leucocytosis recovered without abscess-formation, under large doses of ipecacuanha given at my request, in accordance with the conclusions I had now come to,— that tropical hepatitis, even in the absence of dysentery, is due to latent amœbic infection of the upper colon, and that ipecacuanha is a specific against amœbic disease,

and thus cuts short the source of infection of the liver by healing the amœbic ulcers in the large bowel.

Two years later, in 1907, I was able to record a conclusive series of 13 consecutive similar cases, (the temperature charts of some of which I show you) which sufficed to re-establish, and place on a permanently scientific basis, the preventive method of ipecacuanha treatment to clear up amœbic hepatitis in its early stages, and thus prevent the formation of liver-abscess. This, I shall show you presently, has had a great effect in reducing the mortality of this disease in the British Army in India ever since that date, and it led me to say that any medical officer under whose hands a patient develops an amœbic liver-abscess should question himself how far he is responsible for not having prevented it.

In this connection, it is worth enquiring whether there is such an entity as "tropical liver" apart from amœbic hepatitis, although such is still described in some text books, and even Manson's last edition only recommends ipecacuanha in cases of hepatitis accompanied by dysentery. If any one follows that advice, however, in the Tropics, it will not be long before he has to regret the development of a liver-abscess through the neglect of ipecacuanha or emetine in hepatic trouble, and I urge that no other treatment ought to be applied until that specific drug has been fully tried in all such cases.

Another point which is not yet sufficiently borne in mind, is the fact that there is just as close a relationship between chronic diarrhœa and amœbic hepatitis in the Tropics as with chronic relapsing dysentery, as shown by the diagram of the British Army bowel and liver diseases for 49 years (which I show you), and by the fact that half the fatal amœbic dysentery cases on which I performed post-mortems at the Calcutta Medical College Hospital, had been diagnosed erroneously as "chronic diarrhœa" or "tubercular diarrhœa," with fatally erroneous treatment resulting.

Treatment of Amœbic Liver-Abscess by Aspiration, and Ipecacuanha or Emetine, Without Drainage

I may now return to the rational treatment of an amœbic liver-abscess after the chance of preventing it by early

specific treatment has been lost. From what I have already said, the first consideration is some method of sterile removal of the detritus which the usually fibrous-walled cavity contains, and which in damp, tropical climates excludes the open operation in all but very small abscesses, which are just those most difficult to reach except when bulging in the epigastric region—and those form but a small proportion.

Secondly, but equally important, the specific drug against amœbic disease must be continued after an abscess has formed and is being treated surgically; although I had not found it recommended in any literature I am acquainted with before I pointed this out. An example will best bring this out, such as that of a European patient who had had 4 incisions made in him for liver-abscesses in 4 months, until his side bristled with large drainage tubes. But he still had great pain, fever and weakness, and his surgeon gave him up as hopeless, and told his Indian house-surgeon that he could do anything he liked for the patient. The house-surgeon came to me, and on my advice washed out the wounds with sterile quinine solution, and gave large doses of ipecacuanha by the mouth. The effect was almost magical, for the next day the patient lost all pain for the first time in 4 months; in 3 days his temperature was normal and the discharge was rapidly decreasing; the extensive wounds healed up soundly in 3 or 4 weeks, and he was doing the very hard work of a mining engineer in Bengal a few months later. Such a case speaks for itself; and that reported by Professor Chauffaud, of Paris, of a liver-abscess which had been discharging copiously for several months, clearing up in a few days upon administration of emetine, is equally conclusive.

By the time I got a resident surgeon of the Calcutta European Hospital to try my method of aspiration and injecting a 1 in 50 bihydrochloride of quinine into a liver-abscess, in 1906, I had established the specific action of ipecacuanha in such cases, so I combined the 2 methods, with complete success in 2 cases. In 1910 I was able to record 19 cases, 16 of them the severe cases of large, deep-seated abscesses approachable only through the right ribs, with only 3 deaths, or 12.5 per cent, as against 70 per cent

in the Medical College Hospital at that time; and that, too, although cases containing from 80 to 120 ounces of pus were included in my successful cases.

In my Lettsomian Lectures, of 1921, I was able to collect 2,661 liver-abscess cases treated by the open operation in India and Mesopotamia, the great majority being the comparatively early cases seen in the British Army, with a mortality of 56.8 per cent; and I was able also to record figures of 111 cases treated by my method, almost all advanced ones seen in civil hospitals, with a mortality of only 14.4 per cent, or just ¼ of the open-operation rate.

Only last year a pupil of mine, Dr. K. K. Chathrji, F.R.S.S.I., reported no less than 186 liver-abscess cases treated by aspiration and emetine, combined with irrigation of the cavity through the aspirating canula, with the remarkably low mortality of 1.6%; and if this figure is substituted for his earlier one in my former table, it brings the total collected number up to 264 cases with 6.4%, or only ⅛ of the old rate. As the above figures are all from the same races, from India, and a very few from Mesopotamia, they afford a good comparison of the results of the old and the new methods, although, of course, I am fully aware that some surgeons have obtained better results from the open method since emetine has been in general use. Dr. A. I. Ludlow, for example, has reported 100 cases with only 10 per cent mortality from Corea, with a far better climate than that of Calcutta, although he has recently had 10 consecutive recoveries from my aspiration method.

The good effect of ipecacuanha and emetine in reducing the mortality after the open operation, is also evident from the steady fall in the case mortality, in the British Army in India, from 56.9 per cent in 1,352 cases treated between 1897 and 1906 — before I revived the use of ipecacuanha in hepatitis — to 42.9 per cent in 629 cases treated from 1907 to 1913 before emetine was in general use, and to only 30.0 per cent in 258 cases treated from 1914 to 1919. The average number of cases admitted each year and the rates per mille had also fallen steadily during the same period, as shown in the diagram already mentioned.

The following figures of the Italian Hospital, at Cairo, reported by Dr. E. Gaglio, bring out the same points:

Years	Cases Treated	Re-covered	Died	Case Mortality by Open Operation
1904–1911	64	35	29	45.3% Before emetine
1912–1923	31	24	7	22.6% With emetine

Dr. R. Jelampi also reported, at the Venezuela Congress, the results of his inquiries from several surgeons regarding the number of liver-abscess cases operated on by them and how many they treated by the Rogers method since 1913, the averages working out as follows:

Years	1907–13	1914–19	1919
Average operations (Emetine very limited by war)	17.7	4.7	9

All thirteen replies spoke highly of the aspiration method.

The total reduction in the formerly heavy death rate from liver-abscess in the British Army, is well brought out by the following figures:

Years	Liver-Abscess Mortality per 100,000	
1898–1907	139	Before revival of ipecacuanha treatment of hepatitis
1908–1912	51	After revival of ipecacuanha treatment of hepatitis
1913–1920	19	After introduction of emetine

These data which are shown in the diagram are very satisfactory, and you will see that a sharp fall of the mortality curve of liver-abscess began the year after I published my first cases of successful aspiration of liver-abscess combined with ipecacuanha orally, and that a similar remarkable fall in the number of liver-abscess cases in the army commenced the year after publication of my paper demonstrating that the presuppurative stage of hepatitis could be recognized by the blood-count and that the disease could be cut short by large doses of ipecacuanha.

Lastly, the curve brings out a most extraordinary fall in the proportion of liver-abscess to dysentery cases in the British Army with the establishment of the emetine treatment of amœbic bowel disease, although some years previously there had been a remarkable increase of the ratio,

at a time when the ipecacuanha treatment of dysentery had been very largely replaced in India by the saline treatment, as illustrated by the following average ratios for the years shown:

	Ratio of Liver-Abscess to Dysentery Cases	Ratio of Liver-Abscess Deaths to Dysentery Cases	
1888–1897	1 to 16	1 to 25	Mainly ipecacuanha treatment
1898–1911	1 to 8	1 to 16	Saline treatment
1912–1919	1 to 29	1 to 82	Emetine treatment

Thus, during the neglect of the ipecacuanha treatment of dysentery in India, for every 8 cases of all forms of dysentery 1 developed liver abscess, or twice as many as during the previous era, while with emetine the proportion fell to 1 to 29,— and the deaths, from 1 to 16, to 1 to 82, or under ½.

Few investigators are fortunate enough to be able to point to such satisfactory data, although I am still not quite sure whether these now well-established methods are in quite as universal use as they might be with advantage.

DISCUSSION

Dr. William M. James (Opening the Discussion).— I should like to ask a question. To what do you attribute this remarkable cessation of pain and falling of fever, by the use of emetine in these cases? It seems that it is almost too much to kill all of the amœbas with one or two injections, and yet you do see this remarkable relief.

Sir Leonard Rogers. — In amœbic dysentery cases, numerous amœbæ often disappear within 24 hours after the first injections of emetine have been given, while they are equally easily killed in the vascular liver. This will account for the rapidity of cessation of symptoms of acute hepatitis under the emetine treatment.

Dr. R. W. Runyan (Closing the Discussion of his own Paper).— I was, of course, very much interested to get at last some first-hand information on the aspiration treatment of liver abscesses. I have seen several abstracts, and one article, by Dr. Ludlow advocating this method, but opportunities for trying it are so few and far between in Panama, at the present time, that I have not had occasion myself to try the procedure.

I thoroughly agree with Sir Leonard Rogers' statement that abscess of the liver is a preventable condition; and, since the introduction of emetine in the treatment of amœbic dysentery, I have not seen a single case of liver abscess in which I thought the treatment was adequate. In my paper I failed to mention that of the 21 abscesses of the liver reported in Panama, only one was of local origin. That statement will give you an idea of the scarcity of this class of case in our section at the present time.

Sir Leonard Rogers (Closing the Discussion of his own Paper).— One point I omitted to mention, namely, that in order to prove the value of the use of sterile drainage of liver abscess, I devised a flexible-sheath canula for aspiration, which made it possible to leave the flexible sheath in position in the abscess, and which

connected with a long drainage tube carried down into a bottle of antiseptic, under the bed. In a case thus treated, from which about a pint of pus had been aspirated, the discharge became reduced in a few days to a small amount of clear serum, and the amœbæ disappeared under administration of ipecacuanha. The tube was removed after about 10 days, leaving a 4-inch sinus, which filled completely to the surface in 4 days. The skin healed over 7 days after removal of the tube. This period was less than ⅓ of the shortest time of any similar case treated by the open operation. The case illustrates the importance of having maintained sterility, which is impossible by the open operation in the hot damp Calcutta climate. This method is no longer necessary, now that the efficacy of emetine in these cases is established.

United Fruit Company Hospital at Quirigua, Guatemala

PRELIMINARY REPORT ON THE VALUE OF THE ROENTGEN RAY IN ESTIMATING THE EXTENT OF AMEBIC INFECTION OF THE LARGE INTESTINE

J. J. Vallarino, M.D.

During the past four years, while doing gastro-intestinal examinations in the Roentgen Ray Laboratory of the Herrick Clinic, we noticed the persistent defects which one meets in the large intestine of patients who are affected with amebiasis due to E. histolytica. This became more and more evident until we called them to the attention of our Chief of Medical Clinic, Dr. W. M. James, and demonstrated to him, that while the defects vary in different individuals, there is always present a more or less marked variation from the normal.

The work has been carried on in a more detailed manner during the past eight or ten months, and we have been able to follow a fair number of cases, in which after a clinical and laboratory diagnosis of amebiasis had been definitely established, an examination of the large intestine with the Roentgen Ray was made. This examination was carried on, 24 hours and more, after a barium contrast meal had been taken, or after a barium clysma had been administered, and some times after both; and these cases checked with others without E. histolytica infections, or with amebiasis due to E. coli. The object of the examination was twofold; in the first place we were endeavouring to find out if every case would show intestinal defects, and in the second place to determine the severity of the invasion by the extent of the defects found in the bowel.

Our findings have been very suggestive; first, we found defects in all cases of amebic infection due to E. histolytica, with definite symptomatology, whether mild or severe; and second, the Roentgen Ray findings checked up very well with the clinical findings, in that the filling defects corresponded to the points of tenderness in the abdomen. By this method we were able to determine the extent of the intestinal lesion,

and to give the clinicians data which they could not obtain by any other means, which proved of value in the course of treatment. We were also able in some of the cases to make a reëxamination to determine the improvement in the lesions as compared with the clinical improvement, and found there also, that there was a correlation of the clinical and Roentgen findings. Unfortunately, the majority of these cases that are treated at the Hospital de Panama, come from long distances, and their principal idea is to get better and leave; consequently, reëxaminations that would be of any value at sufficient intervals are very seldom possible, as we get but few local cases.

Forms of Defects. — The defect found in the majority of the cases is a mottling of the affected part; the bowel loses its normal contour and a mottled area is found instead; the extent of the findings depending on the degree of the intestinal lesion. This is tentatively explained by considering that the mucosa of the intestine in this region is ulcerated and inflamed and leaves only a small and irregular part of the lumen of the intestine in which the opaque substance can enter in various densities, which result in the defect found in the film. At other times and particularly in old cases, defects resembling obstructions are found, which may be attributed to isolated patches of infected intestine.

Location. — The lesions are found in the majority of the cases in the cecum and ascending colon, up to the hepatic flexure. The next place in frequency is the sigmoid, and less often we find the transverse and descending colon affected. The great percentage of cases showing defects at or near the hepatic flexure may serve as an explanation in affections of the liver following intestinal amebiasis.

We have found that we obtain better information from our examination by giving the opaque substance by the mouth and then waiting till this substance has reached the lower bowel, when we can take exposures at different intervals, than by administering a barium clysma and then taking exposures at different intervals. The reason for this is that when the opaque substance reaches the large bowel, usually around 24 hours after the injection, it has adapted itself quite well to the surroundings, it has followed the channels which offer least resistance, it has filled pockets and ulcer

C-3. S. A. AMEBIASIS.

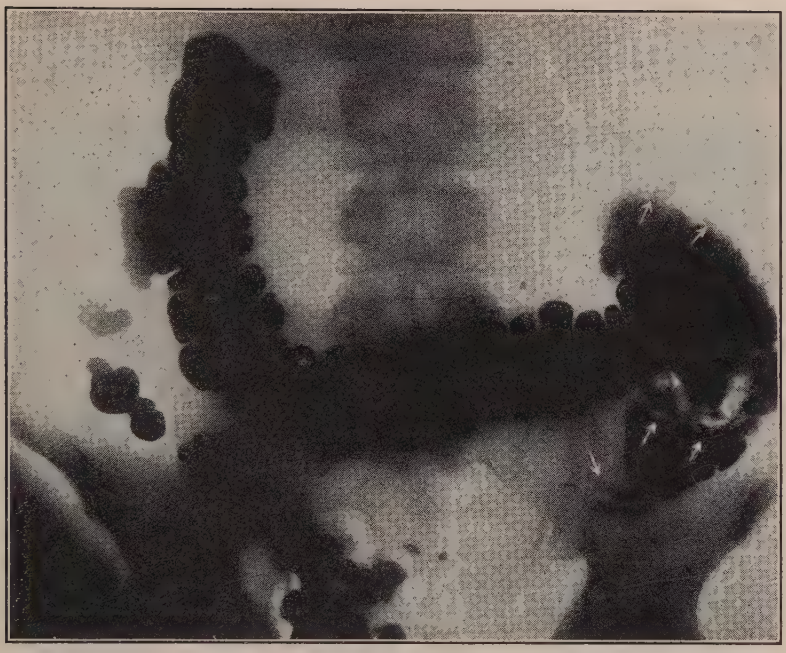
Exposure made immediately after the administration of the Barium clysma. Shows inflammation and ulceration of the cecum, ascending colon and hepatic and splinic flexures.

cavities and is moving under normal propulsion. When an enema is introduced in the large intestine in quantity sufficient to reach the cecum, usually one quart of mixture, there has entered a large amount of foreign substance, under abnormal conditions, propelled against the normal forces by force of gravity, which no matter how trivial, must be enough

C-11. M. M. AMEBIASIS.

Exposure after Clysma. Marked ulceration and inflammation of the cecum, ascending colon, hepatic flexure and descending colon.

to overcome the normal resistance. Under these conditions the bowel becomes abnormally distended, and the ulcers and pockets have not sufficient time to fill properly; that is, for the opaque matter to precipitate in them, and the intestine is making natural efforts to expel this foreign matter, as would be expected from the results of any form of enema; consequently, although the findings after the barium enema are valuable, and the defects are shown well, they lack the



No. 6. J. R.

28 hours exposure. Slight amebic infection with light symptomatology and no history of dysentery. Showing a nearly normal intestine.

clearness and precision of detail which are shown in the other form of examination. The clinical symptoms usually conform with the Roentgen Ray findings. However, this is not always so, and we find sometimes a more extensive ulceration, as indicated by the films exposed, than the clinical symptoms cause us to suspect. On the other hand, we have had no cases with severe symptoms which have not shown a more or less extensive involvement.

No. 9. R.D.S.

Amebiasis with slight symptomatology and no history of dysentery, still shows considerable involvement of the ascending colon and hepatic flexure. Exposure made at 24 hours.

No. 11. T. A.
Amebiasis, with severe symptomatology showing general extensive intestinal ulceration, especially of the hepatic flexure. Exposure at 24 hours, at beginning of treatment.

No. 16. A. M. U.

Chronic severe dysentery. 24-hour exposure. No amebas found. Marked ulceration of intestine at and near hepatic flexure found by Roentgen examination.

THE DISTRIBUTION AND COMPLICATIONS OF AMOEBIC LESIONS FOUND IN 186 POST-MORTEM EXAMINATIONS

Herbert C. Clark, M.D.

The microscopic pathology and morbid anatomy of amoebiasis can be found recorded in detail in all the text-books dealing with tropical medicine. But there are not many records easily available that give a concise idea of the seat of election of the lesions, and the relative incidence of the primary and secondary forms of amoebiasis, with their more important complications. I shall attempt in this report only to reveal the favorite distribution of lesions in the intestinal tract, and the incidence of secondary amoebiasis, with the most important features that were present. Certain other data will also be presented to show the local variations that probably governed the decline of the disease in the population from which the series of cases was obtained.

Through the courtesy of Col. H. C. Fisher, Chief Health Officer of the Panama Canal, these anatomical records were taken from the files of the Board of Health Laboratory of the Panama Canal Zone. The period of time covered is from 1905 to 1923, inclusive. The majority of the post-mortem examinations were performed by Dr. S. T. Darling, a former Chief of the Laboratory, and myself. It is to be noted that the incidence of amoebic abscess of the liver, amoebic appendicitis, rupture of abscesses, and intestinal ulcers, peritonitis etc. seem to warrant some attention. If not impossible, it will at least be difficult to draw satisfactory conclusions from this series in regard to the kind of treatment employed, because the majority of cases were in individuals who arrived at the hospitals in the terminal stage of the disease, and lived only from a few hours to a few days after admission. Furthermore, none of the modern methods of treatment were in use, during a large part of the period of time covered in the collection of the cases. Ancon Hospital treated many of them, while many also came to the laboratory morgue

from the terminal cities (Panama and Colon) as well as from various intermediate points in the Canal Zone, where either they had been under dispensary care or had not applied for treatment at any place.

Race. — The bulk of the population of the Canal Zone and the Isthmus was composed of negroes and Latin-Americans; therefore, it is to be expected that these races should predominate in the series of cases under examination. The numerical proportions were as follows: West Indian negroes, 133; Latin-Americans, 31; foreign whites, chiefly North Americans and Old World Spaniards, 22.

Sex. — Males so far outnumbered the females in the population, from 1905 to 1923, that little significance can be attached to the sex incidence in the series. There were 172 males and 14 females.

Occupation. — The death rate resulting from amoebiasis was very low among the foreign-white population (Old-World Spaniards excluded) as compared with that of the other races. This, perhaps, indicates better living conditions among them, and early attention to any form of an illness. There were 132 laborers, 36 tradesmen, 14 house-workers, and 4 clerks and policemen.

Age. — This is another difficult feature to discuss, since almost the entire population was composed of young and middle-aged adults. The cases appear, chronologically grouped by decades, as follows: —

	Cases
1st decade	5
2nd decade	8
3rd decade	52
4th decade	57
5th decade	44
6th decade	12
7th decade	6
8th decade	2

Treatment Records. — These are offered especially to give an idea of how few cases occurred in the later years of the period, when specific treatment was available, and also to show how many were unrecognized or failed to apply for observation and treatment. Here is the grouping: —

Treatment	Cases
No record of treatment, surgical treatment for abscess or unrecognized	94
Bismuth treatment of some nature	49
Quinine irrigations, opium, and bismuth	21
Quinine irrigations	8
Cecostomy and irrigations	7
Emetine	4
Bismuth and emetine	2
Quinine and ergot	1
Total	186

Past Medical History. — There were 27 individuals with a known history of one or more previous attacks of amoebiasis, who were under treatment for the disease by some physician or hospital.

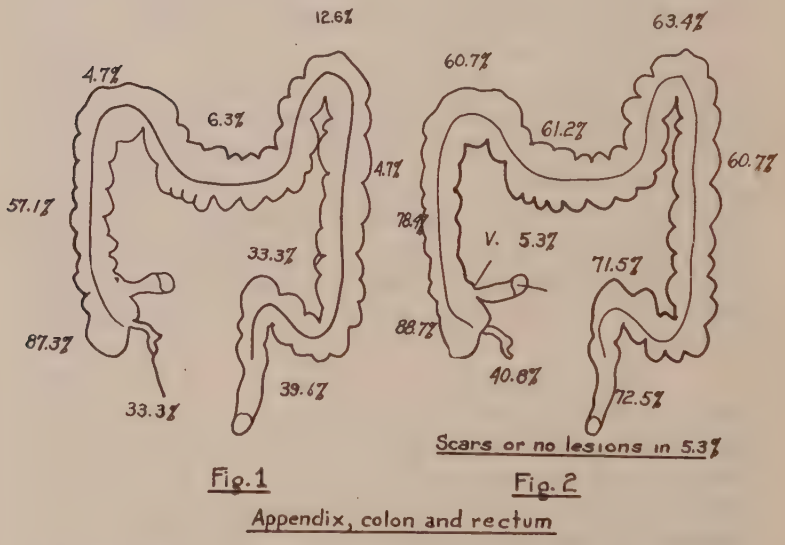
Causes of Death. — The causes of death, as indicated by the autopsy findings in the series, were as follows: —

Causes of Death	Deaths
Amoebic ulcerative colitis (dysentery)	64
Amoebic dysentery and amoebic abscess of the liver	80
Amoebic abscess of the liver (without significant intestinal lesions)	15
Other causes (accidental presence of amoebic ulcers in bowel)	27

Intestinal Distribution of Amoebic Lesions (Primary Amoebiasis). — This can be most easily presented in tabular form as follows: —

Distribution	Times
Entire colon involved	55
Entire colon and ileo-cecal valve involved	3
Entire colon and appendix	48
Entire colon and appendix and ileo-cecal valve	7
Cecum and ascending colon	24
Cecum, ascending colon, and appendix	9
Cecum, rectum, and sigmoid	8
Cecum, rectum, sigmoid, and appendix	6
No primary lesions found in the intestine or appendix	7
Scar or almost healed lesions in the colon	3
Appendix, cecum, splenic flexure, and rectum	2

Distribution	Times
Rectum	2
Rectum and sigmoid	2
Appendix, cecum, both flexures, and rectum	1
Rectum, sigmoid, and splenic flexure	1
Appendix, cecum, and splenic flexure	1
Cecum and ascending and transverse colon	1
Appendix, cecum, and ascending and transverse colon	1
Rectum, sigmoid, and descending colon	1
Rectum, sigmoid, splenic flexure, and cecum	1
Splenic flexure and descending colon	1
Appendix, cecum, ascending and transverse colon, and hepatic flexure	1
Rectum, sigmoid, descending colon, transverse colon, both flexures	1



A more graphic presentation of the distribution can be given by means of the above figures: —

Fig. 2 shows the regional distribution of the lesions in the total of 186 cases.

Fig. 1 shows the regional distribution of lesions in 63 cases in which the ulcers were found in but one or more places in the bowel. This group of cases represents more accurately

the "primary seat of election" of amoebic ulcers, or the locations in which the disease is apt to gain a foothold. Further proof of this, is the fact that most perforations of amoebic ulcers occur in these regions.

Note the incidence in the cecum, ascending colon, rectum, sigmoid, and appendix. The ulcers were scattered throughout the colon in 113 cases (60.7%); they were found in certain regions, only in 63 cases (33.8%); and there were 10 cases (5.3%) in which no ulcers or only scars were found. These few cases revealed, however, some form of a secondary amoebiasis.

The dependent portions represent the regions where the greatest stasis exists in the colon. This affords a favorite resting place for the development of the amoeba. At any rate the incidence of the lesions in these cases, together with the number and character of the ulcers found, tends to indicate that the favorite primary locations for the beginning of the amoebic process are to be found in the following places: cecum, ascending colon, rectum, sigmoid, and appendix. The only dependent loop of the colon, which seems to furnish an exception to the rule in this series, is the middle of the transverse colon.

COMPLICATIONS ASSOCIATED WITH THE INTESTINAL ULCERS

Nature of Complication	Cases
Perforations of ulcers in the colon, site not stated	4
Perforations of ulcers in the caecum, site not stated	3
Perforations of ulcers in the appendix	3
Perforations of ulcers in the rectum and sigmoid	3
Perforations of ulcers in the sigmoid and appendix	1
Perforations of ulcers in the splenic flexure	1
Perforation of ulcers in the sigmoid	1
Perforation of ulcers in the caecum and rectum, walled off	1
Perforation of ulcers in the sigmoid and splenic flexure, walled off, and associated with amoebic appendiceal abscess	1
Appendiceal abscess, amoebic	1
Peri-rectal abscesses, amoebic	2
Fecal fistula, spontaneous, amoebic	1
Fistula-in-ano, amoebic	1

Thus, there were 10.7% of the cases that had suffered a single or multiple perforation of the amoebic intestinal ulcers. Peritonitis of a local or a general nature had resulted.

Abscesses and fistulae were less common, but not very infrequent.

No serious large hemorrhage was found at autopsy, but it was not unusual to find bleeding ulcers and numerous small blood clots. One history indicated serious loss of blood from the bowel.

The 76 cases that revealed amoebic ulcerative appendicitis, resulted in 9.2% perforations or abscess formation. During the period of time from 1910 to 1922, I also received 6 appendices, from the surgical service of Ancon Hospital, in which there were extensive amoebic lesions. Symptoms of dysentery, if not present at the time, were soon associated, except in one case in which the onset of dysentery symptoms was delayed for 2 months. Other appendices were also received, from various surgical services, which did not show an amoebic ulcer, — yet the contents of the lumen or the crypts would contain amoebae.

In about one half of the cases of this autopsy series, where the cases revealed amoebic ulceration of the cecum the appendix was also involved in the same manner. This indicates that the appendiceal location is of importance to the clinician from both the surgical standpoint and the standpoint of carrier possibilities.

It is barely possible that the negro race may show a higher incidence of amoebic appendiceal lesions than some other races, since in their adult life it is not so common to find an obliterative process progressing and closing the lumen. Negroes as a rule, possess a large appendix with a roomy, long lumen. Nevertheless, this race appears to be just as subject as others to congenital variations such as kinks, bands, short meso-appendix, and anomalies of position. A firmly anchored appendix lying in a kinked position forms a bad handicap in the presence of amoebic ulceration.

The fact that the appendix is a rudimentary organ attached to the cecum, which is the favorite seat of election for amoebic ulceration, makes that organ worth a thought as to its carrier possibilities. It does not appear to be a portion of the tract that would be as responsive to treatment as the colon.

LIVER ABSCESS (SECONDARY AMOEBIASIS)

In the series there were 95 cases (51%) showing a lesion of major or minor importance, of this nature. A solitary abscess had developed in 40 cases (42%) and multiple abscesses in 55 cases (58%). Areas of local, acute, plastic peri-hepatitis were present over the location of an abscess, in 79 cases. There were 39 of the cases in which the clinicians had suspected the lesion, and 29 of these had been operated upon.

Amoebic colitis, local or general, was associated in 85 of the cases; 3 revealed scars in the colon, and 7 presented no past history or present evidence of an amoebic process in the intestine or appendix.

POSITION INCIDENCE OF THE LIVER ABSCESSES

Location	Number of Cases	Percentage of Cases
Right lobe	53	55.7
Right and left lobes	16	16.8
All lobes	15	15.7
Left lobe	8	8.4
Location not stated	2	2.1
Right and quadrate lobes	1	1.05

SOME COMPLICATIONS OF THE AMOEBIC LIVER ABSCESSES

Nature of Complication	Number of Times
Rupture of an abscess into the greater peritoneal cavity	9
Rupture of an abscess into the lesser peritoneal cavity	5
Abscess perforating right wing of diaphragm	8
Sub-diaphragmatic abscess, right	3
Abscess perforating diaphragm and body wall	1
Abscess perforating wall of the stomach	1
Rupture of a surgically drained abscess into the vena cava	1
Rupture of an old operative scar for a former drainage of liver abscess	1
Abscess pressure causing obstruction of duodenum and stomach	1
Abscess pressure causing obliteration of gall-bladder cavity	1
Peritonitis, or soiled peritoneal cavity from escaped liver-abscess contents	17

Many of the cases of liver abscess in which the surgeon finds a well-manifested clinical picture of a large local abscess, also have other smaller and deeper abscesses that are not easily found, even if the exploratory needle is used when the liver is exposed during an operation. The usual locations of fairly large abscesses that escape attention, are those which point posteriorly or postero-inferiorly.

Many times the so-called large single abscesses are not, strictly speaking, a solitary lesion, since there is apt to be a zone a centimeter or more in width around the large lesion, which is composed of myriads of very small abscesses. As a rule, when abscesses are scattered throughout all parts of the liver, the lesions vary from the size of a pea to the size of a tennis ball.

Sometimes an amoebic lesion of the liver will contain only a large, dark, hemorrhagic, softened area of necrotic tissue in which are to be found amoebae, — instead of the usual typical abscess with thick, purulent, yellow-green fluid containing ragged, necrotic shreds of tissue.

The average size of the large solitary abscess that attracts clinical attention, is about that of an orange or a grape fruit, and the liver weight will be about 2,600 grams. The largest that I have seen in this series measured 30 cm. by 32 cm. and it caused the boundaries of the liver to be extended from the level of the third rib to the crest of the ilium. The liver weight with the abscess content, was 5,420 grams.

There were five cases — showing a tendency toward healing — of small abscesses, following the drainage of a large abscess by the surgeon. There was evidence of walling off, and the contents were nearly dry.

Another case, which had been given emetine treatment, and in which the liver lesion was not suspected, also showed evidence of retrogression.

OTHER FORMS OF SECONDARY AMOEBIASIS FOUND

Form	Number of Times
Peritonitis (pyogenic form from thin base of unruptured amoebic ulcers)	19
Amoebic abscess of the lung	6
Amoebic abscess of the brain (3 positive and 1 doubtful)	4

Form	Number of Times
Cecostomy wounds showing amoebic invasion	3
Thrombosis, amoebic, of the vena cava and left renal vein	1
Thrombosis, amoebic, of a portal radical	1

The cases of peritonitis mentioned here, though not, accurately speaking, a form of secondary amoebiasis, are the direct result of bacterial invasion through the thin base of one or more unruptured amoebic ulcers of the intestine. There was a single case of lung abscess, in which there had been no perforation of either wing of the diaphragm by the associated liver abscess.

The other instances of the pulmonary lesions were associated with liver abscesses which had been drained by the surgeon, or which had ruptured a wing of the diaphragm. All but one of the brain abscesses were associated with liver abscesses that had been drained by a surgeon. This exception occurred in a male negro, 25 years of age, who died soon after admission to the hospital and was given the clinical diagnosis of chronic nephritis and left hemiplegia. He had no history, nor any symptoms, of a dysentery. The autopsy revealed an orange-sized amoebic liver abscess in the right lobe, several amoebic ulcers in the cecum and ascending colon, and an amoebic brain abscess the size of a hen's egg in the right parietal lobe, extending from the median fissure 2.5 cm. to the right. It was lying chiefly in the cerebro-spinal space, but invaded the pia, the brain cortex, and to some extent the deeper tissues. The roof and contents of the ventricles and the basal ganglia had not been modified.

The locations of the other brain lesions were also in the cerebro-spinal space, with erosion and abscess formations in the following positions: around the pons, medulla, and crus cerebri; right temporal area of the cortex; right parietal area of the cortex. One of the brain cases had an amoebic history of very long duration, his first attack of dysentery dating from as far back as 1898.

The cases of thrombosis mentioned were associated with liver abscesses that had been drained by a surgeon.

Cecostomy wounds through which irrigation treatments are given are apt to become a point for a local secondary amoebic invasion. A large zone around the opening becomes swollen, edematous, and later suppurative in character, and amoebae are abundant in the subcutaneous tissues. It seems quite probable that an operative manipulation can increase the risk of further secondary amoebic extensions; yet the incidence is small, considering the total of cases of liver abscesses treated by the surgeon.

Decline in Number of Cases at Autopsy of Amoebiasis. — In reviewing these records, I found a very sudden decline in the number of cases, following the year 1914. This decline has continued, until it is now a question of only one or two cases a year that pass through the morgue. In order to open discussion as to the probable cause or causes that might explain this result, I shall offer for your consideration some data that belong to the period from 1914 to 1923. First, I shall offer the yield of amoebic cases per 1,000 autopsies performed from 1905 to 1923, inclusive:

	Cases Found
First 1,000 autopsies were performed from Jan. 1905 to May 1907	50
Second 1,000 autopsies were performed from May 1907 to Mar. 1910	61
Third 1,000 autopsies were performed from Mar. 1910 to Mar. 1912	30
Fourth 1,000 autopsies were performed from Mar. 1912 to July 1914	29
Fifth 1,000 autopsies were performed from July 1914 to July 1917	4
Sixth 1,000 autopsies were performed from July 1917 to Nov. 1920	9
Seventh (800) autopsies were performed from Nov. 1920 to Nov. 1923	3

In order to approach the question from a different point of view, I will now give the annual incidence of the cases at autopsy, with the population returns for the regions from which the cases were mainly drawn.

Year	C.Z. Census	Panama City	Colon	Total Population	Cases Amoebiasis
1905	?	?	?	?	10
1906	?	?	?	83,540	31
1907	54,036	33,548	14,549	102,133	35
1908	67,146	37,073	15,878	120,097	17
1909	76,900	40,801	17,479	135,180	12
1910	86,465	45,591	19,535	151,591	16
1911	90,434	46,555	19,947	156,936	18
1912	79,279	47,057	20,174	146,510	17
1913	61,700	47,172	20,232	129,104	10
1914	46,379	53,948	23,265	123,592	5
1915	31,946	60,373	29,331	121,650	2
1916	31,447	60,778	24,693	116,918	1
1917	27,543	61,369	23,386	112,298	2
1918	22,290	61,369	26,078	109,737	2
1919	26,511	61,369	26,078	113,958	4
1920	27,459	60,500	26,078	114,037	1
1921	31,377	60,500	28,789	120,666	1
1922	31,098	...	...	...	1
1923	...	...	...	...	1

These figures were obtained through the Chief Health Office of the Panama Canal and the Board of Health Laboratory of the Panama Canal. They may differ, at some of the periods of time mentioned, from the returns made by the census of 1912, and from the local census made by the Police and Fire departments, but the differences are not sufficient to offer much confusion.

By no means all deaths occurring in the Canal Zone and terminal cities were subjected to autopsy by the Board of Health Laboratory, but a very large number of bodies do pass through that morgue, and about 75% are subjected to autopsy. Therefore, I think that the anatomical records included in this series can be depended on to give a fairly correct idea of the mortality rate of this disease.

A consideration of the changes which took place during the years 1914 and 1915, and which continued in effect throughout the rest of the period, brings to my mind, at present, only four possible factors that might aid in produc-

ing the decline in the mortality rate of the disease. Those factors are: population changes; education in sanitary matters; new and more effective methods of treatment; and the installation of modern water-systems.

Population changes of importance did occur as the completion of the Canal was accomplished, but, though the number of employes of the Panama Canal was reduced, the number of non-employes and of the military forces has been increased, and the terminal cities have shown a steady growth.

Sanitary education, particularly in regard to direct-contact possibilities and soiled food-stuff, has been given more attention.

New treatment, which is more effective in controlling the disease, played an important rôle even before the years 1914–1915, and present methods of treatment offer even more promise.

Water systems of a splendid type were put into operation during the years 1914 and 1915. The Mount Hope water-system was placed in use during the second month of 1914, and supplied the Atlantic side of the Isthmus. During the latter part of 1914 and the early months of 1915, a similar water-system began to supply the Pacific side of the Isthmus. To those who consider water an important vehicle in the spread of the disease, the following facts may be of interest: Prior to the installation of the water systems, 1914–1915, there were 4,000 autopsies, which yielded 170 cases of amoebiasis (4.25%). After this installation, there were only 2,800 autopsies, which yielded as few as 16 cases, or 0.57%.

SUMMARY

Race, Sex, Age and Occupation. — These features appeared in conformity with the character of the population from which they were derived.

Treatment. — A very small portion of these fatal cases were given the present-day methods of treatment.

Past Medical History of Cases. — This was negative or unknown in all but 27 cases.

Causes of Death. — There were 27 cases which died of other causes than amoebiasis, and which had but a few

amoebic ulcers at some point in the colon. Most of the deaths due to amoebic infection resulted from the secondary extension of the disease to the liver, and sometimes to lung and brain. Another large group had a peritonitis that developed from either a perforation of amoebic ulcers in the intestine, or from pyogenic extension through the thin base of an ulcer or of ulcers.

Distribution of Primary Amoebic Lesion. — About 60% of the series possessed amoebic ulcers more or less all through the colon, while about 40% had a local distribution in the more dependent parts of colon and appendix. The local incidence for age and number of lesions can be placed in the following order of importance: — the cecum and ascending colon, the rectum and sigmoid, and the appendix. The results are in conformity, more or less, with the report of Kartulis[1] except in regard to the appendix, which was described as follows: "The appendix was seldom affected (only 9 times out of several hundred cases)."

It is quite true that the appendix is seldom involved alone, but it may take the lead in the clinical picture in some cases and be the cause of some time lapse before the disease of primary importance is discovered. This is a rudimentary organ that tends to become more or less obliterated in adult life, and is subject to congenital kinks, bands, malposition, etc., all of which make it a dangerous position in many cases for an ulcerative process. It seems to me that it might be a more difficult part of the intestinal tract to treat successfully, and this would make its possibilities as a "carrier pocket" even more important in the management of such cases.

Complications of Primary Amoebic Lesions. — Perforations, single or multiple, occurred in amoebic ulcers of the gut or appendix in 10.7% of the series. The majority of these accidents occurred in the cecum, rectum, sigmoid, and appendix. There were two cases showing appendiceal abscesses, two more with peri-rectal abscesses, and two cases with fistulae of an amoebic nature. A spontaneous fecal fistula through the right abdominal wall was found once.

Secondary Lesions of an Amoebic Nature. — Liver abcesses of major or minor degree occurred in 51% of the series.

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[1] BYAM and ARCHIBALD: "The Practice of Medicine in the Tropics," Chap. 62.

Woodward[1] reports 21% in 3,680 dysentery autopsies performed in various tropical countries, while Byam and Archibald[2] state that the liver abscess probably occurs in at least 30% of the cases.

A solitary abscess occurred in 42%, and multiple abscesses in 58%, of the cases. The local distribution of the abscesses was as follows: right lobe, 55.7%; 2 lobes or all lobes, 25.2%; left lobe, 8.4%; unstated location 2.1%.

Peri-hepatitis of an acute plastic nature was present in a focal manner over abscess locations in 83%.

An amoebic colitis, focal or general, was present in nearly all the cases of liver abscess.

Important Complications of Liver Abscesses. — Rupture of one or more abscesses into the greater or lesser peritoneal cavity, happened in 14.7% of the cases.

Rupture of an abscess through a wing of the diaphragm, or formation of an abscess between the liver and the diaphragm, happened in 12.6% of the cases.

Rupture of an abscess into the stomach occurred once.

Spontaneous rupture of an abscess through the body wall was found once.

Pressure from an abscess once obstructed the duodenum and the stomach; there was another instance in which the gall-bladder was stretched out as thin as a ribbon over the prominence of an abscess.

Exclusive of focal areas of acute plastic peri-hepatitis, there was a soiled or infected peritoneal cavity from ruptured abscesses in 17.8% of the cases.

Other Forms of Secondary Amoebic Lesions. — Including all cases of peritonitis from ruptured liver abscesses, all cases resulting from perforations of the gut or appendix, and those cases in which a pyogenic peritonitis developed through the thin base of an unruptured amoebic ulcer, there were 28.6% that showed a serious degree of peritonitis.

The lungs and the brain were the seat of amoebic abscesses 4 times.

Thrombosis, amoebic, of large venous channels happened twice, and each time was associated with a liver abscess case.

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[1] MANSON-BAHR: "Manson's Tropical Diseases," 7th ed., pages 446–447.

[2] BYAM and ARCHIBALD: "The Practice of Medicine in the Tropics," Chap. 62.

Cecostomy wounds were extensively invaded in 3 cases by amoebae.

Decline in Mortality Rate of Amoebiasis. — There was a sharp decline in the number of autopsies showing amoebic lesions, after the years 1914 and 1915. Possible factors that might have been an influence were, population changes, sanitary education, more effective methods of treatment and the installation of a good water-system.

DISCUSSION

Sir Leonard Rogers (Opening the Discussion). — In my paper I have given the results of the numerous post-mortems in Calcutta, particularly bringing out the fact that in most cases of large, single liver-abscess, dysenteric ulcers are limited to the caecum and its neighborhood, and consequently the symptoms are latent and the dysentery is not recognizable during life. This has led old observers to deny the relation of ulcers to antecedent dysentery.

Dr. Foster M. Johns. — I should like to get Dr. Clark's opinion as to the merits or disadvantages of liver puncture for the purpose of diagnosis?

Dr. Herbert C. Clark. — In reply to Dr. Johns, I will say that it is always dangerous for a pathologist to attempt to answer such a question. The pathologist sees only the unfortunate results of exploratory punctures, and does not know how many successful punctures have been made during the period of time required to supply him with one case.

Nearly all the secondary forms of amoebiasis that I have shown you in this series of autopsies have been associated with liver abscesses that have been explored or drained by the surgeon. This may all be coincidence, but it has left me with the impression that if I am ever suspected of having a liver abscess I want the surgeon to open my abdomen and then hunt for the location of the abscess, rather than seek for the lesion with an exploratory needle. If there is no abscess and a needle is used, then the needle wounds certainly will have tended to prepare the ground for an abscess. On the other hand, if there is an abscess present, there is still some doubt as to its extent, size and location, and the best route for drainage.

Thanks to modern treatment, there will be few liver abscesses in the future. I have seen a long series of cases of amoebic dysentery during the last 20 months in Honduras, and not one of them has developed an abscess. Only 2 died — and *they* had perforations in the sigmoid region of the gut, followed by peritonitis.

Dr. H. J. Nichols. — I should like to ask Dr. Clark if he found any evidence of infection of the gall bladder? We had a case in 1916, a medical officer, which was diagnosed as cholecystitis. He was operated upon and a large gall bladder removed which had a leathery wall and contained a pure culture of amoebae. Amoebae were demonstrated in the gall-bladder wall. This officer who had been passing cysts up to this time became cured of a carrier condition. The relation of the gall bladder to typhoid and cholera carriers is well known, and it would be interesting if any observations are available on the gall bladder in amoebic dysentery.

Dr. Herbert C. Clark. (*Closing the Discussion of his own Paper*). — In reply to Dr. Nichols, I must say that I have never seen amoebae in the gall-bladder. We have made it a rule to examine the contents of all gall bladders received from the surgical services, and to examine grossly all gall-bladders at autopsy. When there was evidence of disease, the contents were examined by fresh and stained films, and frequently by culture, but I have never seen amoebae nor the larvae of the *strongyloid* parasite. Several cases of *Clinorchis sinensis* have been found in this way.

Serious external effects on the gall-bladder and ducts have been caused by pressure from a neighboring amoebic liver abscess. The case you have mentioned will stimulate closer observation in the future, to see whether amoebic cysts can be identified.

SYSTEMIC INFECTIONS BY ENDAMOEBA DYSENTERIAE

CHARLES A. KOFOID, Ph.D., LUTHER M. BOYERS, M.D., and OLIVER SWEZY, Ph.D.

The literature of human amoebiasis contains numerous references to the occurrence of organ infection by *Endamoeba dysenteriae* beyond the limits of the colon and the immediately adjacent parts of the small intestine of man. It is known that this organism is found in abscess of the liver (Kartulis, 1887; Osler, 1890; Councilman and Lafleur, 1891*), in lung abscess (Simon, 1890; Grimm, 1894; Osler, 1895; Gauducheau, 1906; Fiaschi, 1898; Bunting, 1906; Artault, 1898; Opie, 1901; Nattan-Larrier, 1907; Potherat, 1911), and has been reported in brain abscess (Kartulis, 1904; Potherat, 1911), from the bladder (Juergens, 1892; McDill and Musgrave, 1905), and in the urine (Posner, 1893; Wijnhoff, 1895), from the testis (Warthin, 1922) and the semen (Hines, 1923) in salpingitis (Menetrier 1910), from abscess of the spleen (Maxwell, 1909), and from malar abscesses (Flexner, 1892; Kartulis, 1893; Verdun and Bruyant, 1907). There are also indications of the association of amebic infection with certain types of iritis (Mills, 1923). We have ourselves found it in the bone marrow in *arthritis deformans* of Ely's second type (Kofoid and Swezy, 1922) and in the lymph glands in Hodgkin's disease (Kofoid, Boyers and Swezy, 1922) and in skin ulcer.

These reported occurrences are of sufficient gravity to raise the question in the minds of pathologists and students of the organism, not only as to the correctness of the amoebic interpretations and of the species of amoebae identified in the tissue invasions (Kofoid and Swezy, 1924) in some of these instances, but also as to the extent to which amoeba has the capacity of invading organs and tissues, and the frequency with which such invasions may occur following infection of the colon. These occurrences also direct atten-

*A few of the earlier records only are here cited.

tion to the method by means of which such invasions might occur: — as to whether amoeba progresses from point to point through the body by direct transit through the tissues, or whether it gains access to these various sites through the agency of the systemic circulation.

The studies upon which the data here presented are based, have been made in the Protozoölogical Laboratory of the University of California, and in conjunction with the Parasitological Division of the California State Board of Health. The studies were initiated in the Army Laboratory in New York City in 1918, and have been continued since that date. A total of over 35,000 examinations of somewhat more than 12,000 persons have been made to date. In conjunction with these examinations, contacts have been established with a considerable variety of types of clinical pictures of amoebic infection, and some opportunities have been afforded for the examination of tissues, such as the appendix, liver, bone marrow, lymph glands, and skin ulcers, as well as the colon, in collaboration with various physicians who have availed themselves of our laboratory service.

The general picture arrived at from this experience tends more and more toward the conclusion that amoebiasis of the colon leads in some unknown degree to a systemic distribution of amoebae by the blood stream, with accompanying localizations of pathological conditions in one or another organ or tissue, and rarely in a more generalized pathological state throughout the body as a whole, especially in cases which culminate fatally and in which a number of organs may be involved. The more widespread pathological conditions become apparent only in the later phases of the disease.

Certain aspects of this problem which cannot be discussed in the brief time at our disposal may be mentioned as significant, although as yet somewhat vaguely apprehended and determined. The first of these is the emergence of a series of distinct clinical pictures of the infection which suggest tissue or organ localization. The organs included in this series are not necessarily only the lung, liver, brain, testis, bone marrow and lymph glands, but possibly also the appendix, the pancreas, thyroid gland, heart, iris and retina.

The second line of evidence is the fact that in a large

percentage of chronic cases of colon infection, and especially when this is accompanied by arthritis or Hodgkin's disease, the amoebic cysts occurring in the stool are wont to be — though not universally — those of the smaller race, generally less than 9 microns, often 5 or 6, and in some instances we have found typical cysts as small as 3 microns in diameter. It is possible either that these represent genetic races of somewhat permanent status (and for this there is no critical evidence) or that they may represent the end result of a long-continued and partially successful serological battle between the host and the invading parasite, in which, perhaps because of contact with bone marrow, or the blood-filtering lymph glands, the amoeba has been gradually transformed into a small type within the history of the individual infection. We have no critical evidence as to which of these two interpretations is the correct one.

Working in our laboratory, Mrs. E. H. Wagener has been able to demonstrate a typical precipitin reaction, using as antigen amoebae from the colon of a cat in which experimental amoebiasis from human amoebae had been established. Efforts to secure complement fixation and a Schick or Pirquet test of intradermal type have thus far failed of accomplishment, because of the difficulty of continuing the infection in culture animals for a sufficient length of time, and of securing material in sufficient purity to make the tests in a critical manner.

It is my purpose in this communication to present the evidence which we have developed in our own investigations of amoebic infection of 3 important territories of the body; namely, the lymphatic glands, the bone marrow, and the skin.

INVASION OF THE BLOOD STREAM IN AMOEBIC INFECTIONS OF THE COLON AND LIVER

In the course of our examination of tissues from necropsies following amoebiasis, we have examined several cases of ulcers of the colon in various degrees of cicatrization. As a general rule, in the older and more cicatrized areas in which there has been considerable fibrosis one finds considerable tracts of the areas involved in which no amoebae whatever can be found, and in general such regions give us less

abundant evidence of tissue invasion than do the smaller, more active regions of ulceration. Through the kindness of Professor Ophuls, of Stanford University Medical College, some excellent material on an active ulcer has been placed at our disposal. A study of the sections of this material not only demonstrates the abundance of amoebae, in the areas of disintegrating glands of Lieberkühn, and especially in the subjacent and more peripheral mucosa, but also shows them in abundance invading the muscularis and even beyond this in the peripheral serosa of the wall of the colon. In this peripheral serosa in which the tissues are not as yet disorganized, although somewhat hypertrophied, one finds many instances of blood vessels in which amoebae are present in quantity, without any local evidence of lesions in their walls. These amoebae are found, not only in the small capillaries, but also in blood vessels up to 0.6 mm. in diameter.

This fact, taken in connection with a well-known tendency of the motile forms of *Endamoeba dysenteriae* in blood, mucus, and pus of the dysenteric discharges of the bowel to feed upon red-blood cells, is indicative of a positive chemotropism on the part of this parasite for either the blood plasma or the red-blood cells.

In certain examples of tissue from liver abscesses, we have been able to find amoebae in the smaller capillaries, in undisturbed liver tissue, as well as in blood vessels in the margins of regions of tissue disintegration in the wall of the abscess. These invasions of the blood stream in the liver are more frequent in the periphery of the area of tissue destruction than elsewhere.

Such observations are indicative of the capacity of this parasite to get into the circulating blood and to travel some distance from the immediate territory of the lesions. The distance to which they go is unknown to us, since our material is limited to the territory adjacent to the ulcer or abscess. Once they are in the blood stream, it is evident that the amoebae might be carried by this current, as are the white-blood cells of similar size, and pass through the heart into the pulmonary circulation and thence into the systemic circulation. They might also, by direct invasion of territories, actively travel to other parts of the organs in which the localization of pathogenic processes occurs.

AMOEBIASIS OF THE BONE MARROW

We had noted for several years, in the course of our routine examinations of persons infected with *Endamoeba dysenteriae*, that there was a surprising number of instances in which symptoms of arthritis were reported as coincident with this infection. In February, 1922, Dr. Leonard Ely, of Stanford University, brought to our attention a type of arthritis which he had designated as Ely's second type of *arthritis deformans*, in which he had been unable to find any concurrent bacterial infection of the diseased joints. Through his courtesy we obtained sections of the excised head of a femur removed by surgical operation and preserved at once in formalin. We found suspicious accumulations of cells in the rather thick celloidin sections submitted to us. He later supplied us with a part of the excised bone. This was refixed in Schaudinn's fluid, decalcified, and sectioned in paraffin. The sections were later stained by us in iron haematoxylin. This femur shows a disturbed histological condition. There is an erosion of the synovial surface, and there are evidences of initial stages of the formation of exostoses near the margins of the eroded area.

This evidence consists of considerable new formation of cartilage and bone. In the central part of the head there is a large necrotic area, in which some of the osseous structure has been destroyed. Surrounding this necrotic area are regions in which there are gathered in local aggregations a number of cells having, in many instances, amoeboid pseudopodia, often hyaline in nature. These are in some instances clustered about the immediate neighborhood of exposed capillaries, and exhibit cytological detail of amoebic nature.

The cytological detail, which is indicative of a nucleus of *Endamoeba dysenteriae*, consists of the rather evenly distributed peripheral chromatin on the inner face of the nuclear membrane, slightly granular intermediate zone, the central or subcentral massive, often spheroidal karyosome which is joined to the periphery of the nucleus by a few spoke radii. All of these structures are siderophile, staining deeply in iron haematoxylin, and in a few instances it is possible to find evidences of a clear halo immediately surrounding the central karyosome.

The nucleus in all of these cells is characteristically and quite persistently spheroidal. There are no cells known to us in the human body whose nuclei have this characteristic structure. The nearest approach to them among the normal cells in the body are the plasma cells, whose cytoplasm lacks the characteristic vacuolation, whose nuclei are less regularly spherical, whose peripheral chromatin is more massively aggregated, and whose karyosome is less definitely central and spheroidal. Such cells, in our judgment, can in all cases be readily distinguished from the cells which we interpret as amoebae.

There remains, however, the possibility that these cells are merely modified leucocytes or connective-tissue cells. We have therefore turned to another criterion for their specific determination. This is, first, the type of nuclear division as exhibited in the mitotic figure, and secondly the number of chromosomes which are characteristic of man and amoeba respectively. By prolonged and intensive search of our sections we have been able to find no less than 13 mitotic figures in various stages of the process of mitosis or cell-division. These all fit into the normal process of division of *Endamoeba dysenteriae* and of other members of the Amoebina, as described by ourselves in recent papers and by others, notably Mathis and Mercier (1916) and Jollos (1917). Our figures cover a larger number of the phases of division than do those of Dobell (1919) and therefore give a very different assemblage of stages. Dobell's figures are, in our opinion, limited very largely to the telophase. His two figures of earlier stages are not worked out with the detail with which ours have been elaborated.

The first of the features which characterize typical amoebic mitosis is the persistence of the nuclear membrane. This is found also in the flagellates, but does not occur in Metazoan mitosis, and thus not in dividing human cells. The second feature is the formation of polar caps, or centrosomes, at the poles of the spindle-shaped nucleus by the migration of the central karyosome to the inner face of the nuclear membrane, where it divides into two daughter karyosomes or centrosomes, migrates to the two poles of the forming spindle, and spins out between the migrating daughter centrosomes a slender, very uniform, siderophile thread,

which has a meridional location on the peripheral membrane. It is therefore best seen in face rather than in lateral view. For this meridional thread we have proposed the name "intradesmose."

The chromosomes appear to emerge for the first time when the karyosome has reached the nuclear membrane. At such time siderophile threads, possibly derived from spoke radii, radiate from it on the nuclear membrane and in some instances are clearly seen to be divided, or at least appear to be doubled. These threads then progressively shorten and are found in later stages scattered near the nuclear membrane, in parallel, angled, or end-to-end position.

At the time of the metaphase, when the equatorial plates form and the karyosomes are at the poles of the spindle, the chromosomes are gathered in a double row near the equator in such a position that they appear to have been divided transversely, whereas in reality their division has been longitudinal, as generally in the cells of plants and animals. Their number, however, is now double that of the normal number. In *Endamoeba dysenteriae* this normal number is 6. We thus have 12 chromosomes in the completely doubled equatorial plate.

In the anaphase the 6 daughter chromosomes migrate toward each pole, and in the following telophase mass together around the polar centrosome. The telophase is completed by the pinching apart of the nucleus into 2 sections, by an equatorial constriction of the nuclear membrane and a later segregation of the chromatin material in the peripheral chromatin and the central karyosome.

The contrast between the process of mitosis in the amoeba in the bone marrow, and that in human cells, will be revealed by the comparison of our account with that detected in human lymph-cells in lymphatic glands, in Hodgkin's disease. In human cells, at mitosis, the nuclear membrane entirely disappears. The poles of the centrosomes in the human cell are joined together, not by a meridional paradesmose, but by an axial bundle of delicate threads, the centrodesmose. Furthermore, the human cells have 48 chromosomes as compared with 6 characteristic of *Endamoeba dysenteriae*. There is no possible confusion between the 2 types of cells at mitosis.

There remains a possible source of error, in that abnormal human cells might present a picture such as that which we have set forth in the dividing amoeba. However, these cells which we interpret as amoebae appear to be perfectly normal, and the process fits precisely into the picture of dividing amoeba in cysts and in the motile stages elsewhere; and they do not present the immense variety in the nature and configuration of the chromatin material which is so characteristic of abnormal mitosis in human cells.

It is a matter of some interest and significance, in this connection, that in the course of over 35,000 examinations of more than 12,000 people we have found a very considerable number of coincidences of *amoebiasis* and *arthritis deformans*, and these rheumatic symptoms and exostoses are reduced and in some instances disappear on treatment for amoebiasis.

HODGKIN'S DISEASE

In 1921 Dr. L. M. Boyers, of the University of California Infirmary, in Berkeley, brought to our attention the stool of Mr. S., whose case had been diagnosed in Melbourne, Australia, as Hodgkin's disease. Sections of an excised gland from this case were later received and, together with the clinical symptoms, clearly established a condition of typical Hodgkin's disease. Examination of the stools brought to light coincident amoebiasis. Treatment for amoebiasis was followed promptly by signs of improvement, including reduction of the glands. Later the patient died of nosebleed while en route to Melbourne, in Tahiti.

Since that date, 20 cases of Hodgkin's disease diagnosed by competent pathologists and clinicians have been examined by us for amoebiasis, with the result that the cysts of *Endamoeba dysenteriae* have been found in the stools of a total of 18 cases. In one of these exceptions, only a single stool was available, and in the other we made 6 examinations, with negative findings, just prior to the fatal termination of the disease. In nearly all of these the types of amoeba found are of the smaller race, generally less than 10 microns in diameter, and in not a few of the cases it was necessary to continue the search over a number of days, or even several weeks, before the cysts could be located in the stool.

The proportion of motile amoebae of small size present in

stools containing the cysts, was rather large in some of the cases. This degree of coincidence is highly suggestive, on a statistical basis, of a causal connection between Hodgkin's disease and amoebiasis. Assuming an incidence of amoebiasis among the general population to be 5%, and that the mortality due to Hodgkin's disease as stated in the U. S. mortality tables is reliable, the statistical probability of a causal relationship is considerable.

We have been able, to date, to make examination of an excised cervical and of an inguinal gland, respectively from 2 cases of Hodgkin's disease. Our examination is not completed in several other instances, but in these 2 in which the glands were of small size, not more than 2 cm. in longest diameter — and still in the soft stage before fibrosis had progressed to any considerable degree — we have found cells which we interpret as *Endamoeba dysenteriae*. These are all naturally in the motile phase, and are in consequence of this somewhat like certain leucocytes or plasma cells of the human body.

The question naturally occurred to us as to whether we might not be dealing merely with connective tissue cells or leucocytes in modified form, resulting from the pathological state of the tissue in which they were found. We were suspicious that they were amoebae in the first place because of very slight differences in the stainability of a number of them, even in iron haematoxylin, and in the marked sphericity and uniformity of their nuclei, and secondly because of the structure of these nuclei. They were typically amoebic in type, having uniform or blobbed peripheral chromatin, slightly granular intermediate zone, occasionally a clear karyosomal halo, and a central or subcentral spheroidal single karyosome, from which a few spoke radii pass to the peripheral chromatin. The cells of the human body to which this type of nuclear structure most nearly approaches, are the plasma cells; but their structure is sufficiently different, because of the larger chromatin masses of the nuclei of the plasma cells, and their lack of sphericity, and the irregularities of their karyosome, so that it seems improbable that we are dealing with plasma cells.

These amoebae were found either near the periphery of the gland, or in and about the area of cellular disorganiza-

tion in the center of the gland. They were never abundant and were found only by prolonged search.

As a final proof of their amoebic nature, we were able to find a number of instances of nuclei in one or another phase of mitosis. These phases fit precisely into the scheme of nuclear division, as we have worked it out in the nuclei of the cysts of *Endamoeba dysenteriae*, and also in *Endamoeba coli* and *Councilmania lafleuri*. This type of division is characterized by the migration of the central karyosome to the periphery, and its subdivision into two migrating polar caps or centrosomes, which pass to the poles of the spindle and, as they separate, spin out between them the intradesmose, a meridional thread of siderophile nature. The chromosomes, in the meantime, emerge perhaps in conjunction with the spoke radii from the peripheral chromatin, splitting while still in this peripheral position, and shortening into stout rods in an end-to-end position on the equatorial plate. The nuclear membrane remains intact during the process, and the chromosomes are approximately 6 in number, never 48 as in human cells dividing in the same gland. The picture of mitosis in such human cells is characteristically very different from that seen in these amoebae.

A number of the amoebae stain deeply and diffusely in the iron haematoxylin, as though the nucleus were in an abnormal condition. This suggests that possibly the amoebae are being continually destroyed in this tissue, and whatever endotoxins they might possess would thus be released in this territory of a chronic inflammatory process.

Since this conclusion was arrived at, Dr. Boyers has treated one case (over a year ago) which has shown very marked improvement. Dr. Lambright of Columbus, Ohio, has treated another case with similar results, and observations on still other cases are in progress. We infer from these data that Hodgkin's disease is amoebiasis of the lymphatic system, and that amoeba arrives at these locations in the body by the systemic circulation, or possibly through the lymphatic system.

Endamoeba Dysenteriae IN SKIN ULCERS

On October 24, 1922, Drs. E. Von Adelung and P. F. Abbott, of Oakland, California, brought to our attention a

serious case of amoebic liver abscess which had received surgical treatment. This case was later accompanied by the appearance of erythematous spots upon the limbs and trunk, and a margin of like appearance around the region of incision. These spots enlarged until they reached, in some cases, a diameter of 20 mm. Each spot was circular in shape, had a necrotic central area with a dark margin immediately around it, and an erythematous ring outside of this, which paled into the normal skin.

The case terminated fatally. It was impossible, however, owing to legal difficulties, to obtain a necropsy until 4 days after death. The tissue in the margin of the area of incision and of the spots upon the limbs, were secured for microscopical examination and preserved by the usual methods. Portions of the liver were also secured for examination of the margins of the abscess.

The liver tissue exhibited the conditions typical of amoebic liver abscess, and amoebae were found in the tissue adjacent to the abscess. The clinical history and pathological state of the tissues and the presence of the amoebae, confirm the diagnosis that this was a case of typical amoebic abscess.

Sections from small ulcers in the early stage of their emergence in the skin, show a disorganization of the tissues in the center of the area and an accumulation of pigment in the connective tissue cells about this center. Scattered sparsely throughout the central area and accumulated in large numbers in the margins of the greatest tissue disturbance, are to be found a number of cells which we interpret as amoebae. These have undergone, in many instances, in consequence of the delay of necropsy, considerable nuclear disorganization, and have the typical size, general form, cytoplasmic appearance, and spherical nuclei characteristic of *Endamoeba dysenteriae*. In many instances the chromatin has undergone considerable disorganization, but in a few cases in otherwise typical amoebae the nucleus has the characteristic form of that of *Endamoeba dysenteriae* with peripheral chromatin, central karyosome and spoke radii. On comparison with the amoebae in tissues, we have not the least doubt that we are dealing here with *Endamoeba dysenteriae*. These amoebae in this territory occur both in capillaries of small blood vessels, and free in the tissues.

In 1921 Drs. M. F. Engmann and A. S. Heithaus published an account of *Amoebiasis cutis* occurring in a fatal case of human amoebiasis, in St. Louis. They reported the finding of cells which they interpreted as amoebae, in the ulcers that developed on the body of this patient. Through the kindness of Dr. Engmann we have examined his slides stained in toluoidin, and have made preparations from his specimens of imbedded tissues, staining the same in iron haematoxylin.

We have found, both in his original microscopic preparations, and in those which we have made, cells in the tissue, in the margins of the ulcers, which are undoubtedly *Endamoeba dysenteriae*. They have the typical appearance of amoebae in the tissues, and exhibit the nuclear structures which characterize this species.

It is interesting that ulcers of this phagedenic type, with dark margins, peripheral borders, and undermined margins, are figured in some of the early illustrated works upon skin diseases of man.

Nasse (1891) apparently found amoebae in a case of hospital gangrene associated with liver abscess. Selenev (1909) reports a case of *dermatitis desquamatous pustulosa* of amoebic etiology. Menetrier and Touraine (1908) and Bassères (1911) have also each reported a case of cutaneous amoebiasis following operation for amoebic abscess of the liver. Carini (1912) has also reported a case of cutaneous amoebiasis.

THE ROUTE OF TISSUE INVASION

The facts that *Endamoeba dysenteriae* in the motile stage in cases of active amoebic dysentery, often gorges itself with red-blood cells, and that it occurs in such numbers in capillaries of the smaller blood vessels of the colon, in peripheral areas around ulcers, both suggest that this organism has a positive chemotropism for erythrocytes, or possibly for the blood serum in which they are found.

In this respect this parasitic amoeba of man stands in sharp contrast to all other species parasitic in the human bowel, except *Councilmania lafleuri*, which occasionally, in cases of active ulceration accompanying infections by *Endamoeba dysenteriae*, is found feeding upon red-blood cor-

puscles. No other species has been found by us with red-blood corpuscles in its food vacuoles. Statements that *Endamoeba coli* occasionally feeds upon red-blood corpuscles are, in our opinion, based upon observations on *Councilmania lafleuri*, and not upon *Endamoeba coli*.

Amoebae which have entered the circulatory system in the wall of the colon might easily be carried in the blood stream, in blood vessels of the proper size, to any part of the body. It is quite probable that they would tend to lodge in smaller capillaries and in areas where the circulation is the least active. Hence it is to be expected that the lymph glands, the bone marrow, and the spleen would be peculiarly subject to invasion, and that the capillary net of all organ systems would become areas of temporary or permanent infiltration of amoebae.

Permanent establishment of amoebic infection with pathological consequences perhaps might be facilitated or accelerated by concomitant bacterial infections, or by functional disturbances which influence serological states, by local immunological reactions, or by the state of the tissues into which the amoebae are carried by the blood stream.

The size of the infiltering amoebae doubtless has some bearing on the facility with which they enter some of the blood vessels, although this might not in any way affect their capacity to traverse the tissues directly. In the course of our stool examinations, we find that the so-called smaller races of *Endamoeba dysenteriae* are more generally found in chronic cases of amoebiasis whose clinical history suggests long-standing infection. This is especially true of cases of *arthritis deformans* of Ely's second type, and of Hodgkin's disease, as well as of many cases of chronic, low-grade ill health.

In such clinical types of amoebiasis the size of the cysts in the faeces is generally less than 10 microns, often 7 to 9 sometimes 6 to 8, and in rare cases from 3 to 5 microns. These sizes of the cysts give us ground for the inference that the motile amoebae, some of which we find have measured 10 microns, are also of very small size; so that with slight elongation they could travel through any capillary through which an erythrocyte could pass. In this connection it is of interest to note that Gauducheau (1906) reported the

production of amoebic dysentery by the intravenous inoculation of pus from a liver abscess.

We know all too little, from observation of amoebae in tissues, of the degree to which tissue-invasion occurs, especially as to whether or not there is any phenomenon of tissue or organ acclimatization. The clinical facts of liver abscess, lung abscess, brain abscess, bone-marrow infection, and Hodgkin's disease, indicate at least a predominant or extensive infection in definite organs of the body. The concomitance of skin ulcers and liver abscess is to be noted in this connection. As a general rule, there is little evidence that tissue invasion by amoebae results in destructive pathological conditions in several parts of the body at one time. Inspection of the bowel by the proctoscope, in cases of arthritis, reveals no ulcers but colitis with a mottled surface and pin-point areas of inflammation in the lower bowel. Clinical signs of extensive invasion of the colon elsewhere may be very slight, or even lacking, at the time of the physical examination. Generally, however, there is a clinical history of long-continued intestinal disturbance. It seems probable, therefore, that the portal of entry is in all cases, as might be expected, the wall of the colon, and that the route is thence into the blood stream to other parts of the body.

There is, then, it seems, some indication from the clinical examination of cases that there may be in man, in cases of infection by *Endamoeba dysenteriae*, some degree of tissue or organ acclimatization. Experimental infections on culture animals will be needed, however, to establish any such hypothesis. Rosenow's results relative to organ acclimatization with streptococcus are suggestive in this connection. A widespread interest on the part of the medical profession in an intensive study of the clinical aspects of human amoebiasis, and the coöperation of the pathologists and protozoölogists in the investigation of material available at necropsy, are most essential in arriving at any complete picture of the nature, extent, and consequence in the human body of an infection by *Endamoeba dysenteriae*.

In conclusion, we may summarize that conception of the nature of the infection which has developed in our study of human amoebiasis, as follows:

SUMMARY

From its portal of entry through the epithelium of the colon into the submucosa, *Endamoeba dysenteriae* tends to spread in the margins of ulcers of the colon into capillaries and smaller veins, and thence may make its way into the capillary net of the liver, through the heart to the capillary net of the lung, and thence into the systemic circulation. Liver, lung, and brain abscesses are thus to be interpreted as haematogenous invasions by way of the blood stream, rather than by direct movement of motile amoebae through the tissues. Infection of bone marrow will also follow by this route. Whether or not the infection of the lymphatic glands occurs by the lymph stream or by the arterial system, is unknown. The agency of the latter system is suggested by the occurrence of amoebae in the periphery of the infected glands.

Clinical suggestions of pathological conditions in the iris and retina of the eye and in the thyroid, and the occurrence of amoebae in the testis, semen, spleen and skin ulcers afford additional evidence of generalized distribution of this parasitic organism. The limitations of destructive pathological action, in conjunction with amoebae, to single organs such as the liver, or the lung, or the brain, suggest organ acclimatization; and infections of the bone marrow and lymphatics are similarly suggestive of tissue acclimatization. The picture as a whole is rather strongly indicative of an affinity on the part of this parasite for the mesenchyme and the organs formed therefrom, especially for the connective-tissue regions such as the framework of the glands, and the tissue derivatives of the mesenchyme, such as the blood system, the bone marrow and the lymph glands.

The importance of continued clinical study in correlation with examination of tissues at necropsy and, when available, at surgical operations in cases of amoebiasis is most evident. It is also highly important that intensive clinical studies be made, in order to differentiate and establish with greatest possible clearness the fundamental clinical picture of amoebiasis, especially in temperate regions. The more highly specialized and peculiar modifications of this picture dependent upon localized infections in various organs of the

body, also call for clinical study and for vigilance in their detection. Systematic stool-examination for infection by *Endamoeba dysenteriae* will be of greatest assistance in directing the diagnostician's attention to the possibility of complications by this widespread parasitic infection of man.

The observations on the invasion of various organs and tissues of the human body by *Endamoebae dysenteriae*, the extraordinary variety of clinical aspects of the disease which these invasions create, and especially the linking of amoebiasis with constipation and certain forms of rheumatism and its probable connection with the widely prevalent mild type of chronic invalidism in middle age and thereafter — all these factors create an interest in the mode of infection of this communicable disease. They also lead to an interest in the methods of its prevention.

Our data of occurrence in over 12,000 persons lead us to infer that it is age-old and race-wide, and the product of evolution. It is therefore not peculiar to the Tropics, although its prevalence is accentuated there by ignorance, lack of sanitation, and travel. Its occurrence in the temperate regions may be increased by the return of infected persons from areas where contacts with the infection are more frequent.

The modes of infection seem to be solely by the resistant cysts which are discharged in the faeces and may contaminate food or water. The agencies by which this contamination are brought about are the soiled hands of the infected food-handler, and the fly which feeds upon human faeces and deposits the unharmed cysts in the kitchen or elsewhere upon food or in milk. Consequently family infections are very frequent. If either parent has acquired the infection, it is not infrequent to find the disease spreading to the other parent and the children of the family. Water or dust appears to be relatively less important as an immediate agency in spreading the disease, than is contact with the infected food-handler.

Practical measures which may be of service in the reduction of this widespread infection of man are the treatment and cure of chronic carrier cases, obliterating centers of infection. Means of protection against such centers, on the part of those who travel, are the use of running water and

the shower bath to avoid oral contacts with cysts while bathing, and the reduction, so far as feasible of the amount of uncooked food, especially salads, strawberries and other forms of fruit and vegetables subject to contamination from infected soil. Public measures, such as proper sewage disposal and the legal restrictions on the use of night soil in gardens, will also aid. It may be that in time the examination of food-handlers in public establishments like hotels and restaurants, will be adopted as a measure of service in the protection of patrons. Such examinations might well include not only inspection for typhoid but also for amoebic carriers. Since travel is destined to increase with the improvement of facilities and opportunities, it is evident that exposure to faecal-born infections of infected food-handlers will increase correspondingly.

A campaign for cleanliness and the education of the public in the meaning and significance of the infections derivable from human faeces, will be of assistance in both the elimination of carriers and the establishment of protective measures.

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DISCUSSION

Dr. Aldo Castellani. — I should like to make a few remarks in connection with Dr. Kofoid's very interesting address. Professor Kofoid rightly calls attention to the fact that amoebiasis may attack practically any organ or system of the human body. I venture to remind this audience of the fact that most of the conditions so ably described by Professor Kofoid have already been put on record, and may be found in any modern text-book of tropical medicine. I should like to call attention to the so-called "tropical liver," to "Bronchial amoebiasis" and to "Amoebic fever."

Sir Leonard Rogers and I independently pointed out, some time ago, that the so-called tropical-liver is in reality a form of amoebiasis, as hystolytica cysts are often found in the stools in such cases. Chalmers and I some years ago, at a meeting of the Ceylon Branch of the Medical Association in Ceylon, called attention to cases of bronchitis after dysentery and hepatitis, in which the administration of ipecac, was extremely useful.

In cases of what I call amoebic fever, the only symptom which the patient presents is fever, the examination of all organs being negative; this fever is apt to be mistaken for malaria but will yield only to emetine, or ipecac in large doses.

THE CONTROL OF INTESTINAL PROTOZOA BY MEANS OF CHANGES IN DIET

ROBERT W. HEGNER, Ph.D.

The digestive tract of mammals has long been recognized as a favorable habitat for many genera and species of protozoa. The protozoan inhabitants of man are better known than those of any other mammals; they include representatives of all 4 classes of the phylum. With the exception of 2 species, the flagellate, *Trichomonas buccalis*, and the amoeba, *Endamoeba gingivalis*, which live in the mouth, all of the protozoa of the human digestive tract live in the intestine. At least 5 distinct species of amoebae live in this habitat, *Endamoeba histolytica*, *E. coli*, *Endolimax nana*, *Iodamoeba williamsi* and *Dientamoeba fragilis*. A number of other species of amoebae from the digestive tract of man, have been described but cannot be considered at present well established. Five distinct species of flagellates occur in the human intestine, *Chilomastix mesnili*, *Trichomonas hominis*, *Embadomonas intestinalis*, *Enteromonas hominis*, and *Giardia lamblia*. Five species of coccidia have been described from man, *Isospora hominis*, *Eimeria wenyoni*, *E. oxyspora*, *E.* (?) sp., and *E. snijdersi*. The coccidia, however, are really tissue parasites, although they are often erroneously included among the intestinal protozoa because their oöcysts pass out of the body in the feces of the host. The only ciliate that is known with certainty to be an inhabitant of the human intestine is *Balantidium coli*.

Some of these protozoa, such as *Endamoeba coli*, live within the lumen of the intestine, where they feed on bacteria, starch grains, and plant debris. Others have more or less constant access to the intestinal wall, such as *Giardia*, which possesses a sucking disc by means of which it attaches itself to the epithelium. Here it lives on material that it absorbs through its walls. *Balantidium coli* usually lives in the lumen of the intestine, feeding on all sorts of small particles, but occasionally penetrates the mucus and enters the mucous and submucous tissues where small colonies are formed and

ulcers produced. A more constant association with living tissue is characteristic of *Endamoeba histolytica*. This species apparently feeds only on tissue elements and, while it usually does not bring about clinical symptoms, sometimes penetrates the tissues, giving rise to diarrhoea, dysentery and other generalized effects. Finally the coccidia probably live throughout their lives in the tissues of the liver or the intestine, except during the early stages when the sporozoites are penetrating the tissues, and during the last stage when the oöcysts are liberated from the body of the host. They are not intestinal protozoa in the same sense as the other species mentioned above, and are hence omitted from further discussion.

The importance of these intestinal protozoa may be measured by their incidence of infection and their pathogenicity. There is no question, I believe, but that *Balantidium coli*, and *Endamoeba histolytica* are pathogenic. The other species appear to be non-pathogenic with the possible exception of *Chilomastix mesnili*, *Trichomonas hominis*, and *Giardia lamblia*, which are often accused of causing "flagellate diarrhoea." Opinion is divided regarding these three species.

Several years ago Dr. George C. Payne and I reviewed the findings of a number of English, French, and American investigators who had examined both healthy and diseased persons, mostly soldiers. Only the more common species of intestinal protozoa were reported and not all of the work was as thoroughly carried out as might be desired, but the results give a general idea of the incidence of infection. The data show that healthy persons, as well as those suffering from intestinal disturbances, are highly infected, and that intestinal protozoa are widespread in their geographical distribution. The percentage of infection was found to be approximately as follows: *Endamoeba coli*, 20 per cent; *E. histolytica*, 9 per cent; *Giardia lamblia*, 12 per cent; *Chilomastix mesnili*, 4 per cent; and *Trichomonas hominis*, 3 per cent.

The most recent large survey of intestinal protozoa is that carried out by Boeck and Stiles. These workers examined 8,029 persons, 2,584 of whom were home-service troops, 3,536 had been in foreign service, and the remaining

1,909 were chiefly residents in asylums, hospitals, and other institutions. The results show an infection with *Endamoeba coli* of 19.6; *E. histolytica*, 4.1 per cent; *Endolimax nana*, 13.2 per cent; *Iodameba williamsi*, 5 per cent; *Giardia lamblia*, 6.5 per cent; and *Chilomastix mesnili*, 3.1 per cent. *Trichomonas hominis* was recorded from only 6 cases. This was probably due to the fact that much of the material examined came from a distance and only cysts survived, so that this species which is not known to form cysts was eliminated. No survey comparable to that of Boeck and Stiles has been made in the Tropics, but there is no reason to believe that intestinal protozoa are less widely spread or less abundant in warm countries than in the colder regions of the earth.

Many species of intestinal protozoa similar to those known from man, live in lower animals. A review of the literature indicates that herbivorous animals are particularly highly infected. Ungulates such as horses, cattle and goats are abundantly infected with ciliates and also harbor flagellates and amoebae. Rats, mice, guinea pigs and other rodents are usually infected with several species of flagellates and amoebae. Omnivorous animals are often infected, but with fewer species. Of these animals the primates are of particular interest because of their resemblance to man. Two genera of ciliates, *Balantidium* and *Troglodytes*, and several species of amoebae have been reported from them and I have recently found cysts of both *Chilomastix* and *Giardia* in the stools of South American monkeys.

In contrast to the conditions observed in herbivorous and omnivorous animals are those that apparently exist in strictly carnivorous species. Not a single ciliate has been reported from carnivorous mammals and only rarely have infections been noted with intestinal flagellates and amoebae, and in these cases the hosts have been dogs, cats or foxes which, although carnivores, were really living on a largely vegetable diet. It would be interesting to make a survey of intestinal protozoa of a group of meat-eating men such as the Eskimos. I venture to predict that no infections would be discovered.

Fortunately the relations between a carnivorous diet and the presence of intestinal protozoa are open to experimental

study. My attention was first attracted to the problem by the discovery of 3 rats among those in Dr. E. V. McCollum's colony that were entirely free from giardias and trichomonads and had been fed on a carnivorous diet throughout their entire lives (174 days).

Rats from my own colony that were fed largely on a carbohydrate diet were then subjected to experimental conditions; 15 control rats were all found to be abundantly infected with giardias and trichonomads; 15 others were fed on a carnivorous diet for 7 or 8 days and then examined. It was found that giardias were absent in 7 per cent of the latter and had decreased in number in those rats in which they were present about 90 per cent, and that trichomonads likewise were absent in 7 per cent of the experimentally fed animals and had decreased in number in the others about 98 per cent. What caused this rapid disappearance of these flagellates is not definitely known, but it is suspected that the change from a predominantly acidophilus type of intestinal bacteria to a predominantly putrefactive type brought about an environment unfavorable for the trichomonads. No satisfactory explanation has yet suggested itself to account for the decrease in the numbers of giardias.

Whether or not a carnivorous diet has as unfavorable an effect upon human intestinal protozoa as upon those of lower mammals remains to be determined. The study of this subject promises to answer not only this question but also that of the pathogenicity of such species as *Giardia lamblia*, *Trichomonas hominis*, and *Chilomastix mesnili*. If these flagellates in cases of "flagellate diarrhoea" can be eliminated by the administration of a carnivorous diet, and if at the same time clinical symptoms disappear, it seems probable that these symptoms were brought about by the flagellates. This problem can only be studied by physicians who have long-continued control of patients, but the evidence that I have gathered indicates that certain intestinal protozoa of man can be controlled by changes in diet.

Trichomonas hominis and *Chilomastix mesnili* seem to me to be species that might most easily be affected since they live chiefly in the large intestine where they would be subjected to changes in bacterial content and the products of bacterial decomposition. Dr. T. B. Magath, of the Mayo

Clinic, has tested a carnivorous diet on several diarrhoeic patients with infections of these flagellates and has noted either an extremely marked diminution in the number of flagellates or apparently a total riddance of them. I have been able to observe the effects of such a diet on one patient suffering from diarrhoea and infected with *Trichomonas hominis*. Both the flagellates and diarrhoea disappeared entirely 3 days after the treatment was begun, and no symptoms nor flagellates had reappeared 32 days later when the patient left the city. Several other patients suffering from diarrhoea and infected with giardias and trichomonads are now taking this treatment, but it is too early to report definite results.

The data presented above show that carnivorous animals are very rarely infected with intestinal protozoa; that a carnivorous diet is unfavorable to the giardias and trichomonads of rats; that a carnivorous diet may also be unfavorable to these flagellates in man; and that *Giardia lamblia, Trichomonas hominis* and *Chilomastix mesnili* are probably the real etiological factors of "flagellate diarrhoea." Whether other changes in diet might have similar results is yet to be determined, as are also the effects of a carnivorous diet on the intestinal ciliates and amoebae of man. Intestinal disturbances are particularly prevalent in the Tropics, but how frequently they are accompanied by protozoa in the digestive tract is unknown. The situation offers an interesting and profitable opportunity for observational and experimental work.

DISCUSSION

Dr. Charles A. Kofoid (Opening the Discussion). — Several interesting experiments have been made in our laboratory by Dr. J. F. Kessell, now of Peking Union Medical College, bearing on this matter of diet with reference to human intestinal amoebae. We were endeavoring to establish infections of these amoebae, using rats and mice in the hope that we might establish amoebiasis and get ulceration. We found after long experimentation that it was necessary to relieve the rats and mice of their own amoebic infections before we could establish the human amoebae in them. Finally we learned that, if we took young rats determined to be amoeba-free by purging with epsom salts, human amoebic infec-

tions could be established. Autopsy confirmed the reliability of the epsom-salt method.

We also learned that it was impossible or impracticable to infect young rats while they were still nursing, and that rats on a milk diet would often free themselves from amoebic infections. We have here confirmatory evidence that modifications in diet do serve to reduce the amount of protozoan infections other than flagellates. It is well known to protozoölogists that vegetable-feeding insects, especially Hemiptera, fishes and rodents, are heavily infected with flagellates. Carnivorous fishes and insects are not thus heavily infected. Plant-feeding mammals are almost universally infected with Protozoa.

We had one very interesting case of heavy infection by Giardia. The patient himself was intelligent and very much interested. He felt that he knew there was an interesting relation between his symptoms and the abundance of the flagellates. He claimed that honey introduced by the duodenal tube would greatly reduce the flagellate infection by Giardia. I don't know how true this was. We find that in the rat the intestinal amoebae go to the caecum and that this region has a larger percentage of infection than the colon, and a higher degree of acidity than the colon.

In the matter of the flagellate infections of man, I wish to direct your attention to a seemingly tropical type of trichomonad infection due to Pentatrichomonas. We have had 4 cases under observation for a series of months, and in one instance for several years. All of them were serious, having chronic diarrhoea with sometimes as high as 20 stools a day. One of the patients is a colonel in the United States army, with tropical service; one is from Hawaii; one an officer with contacts with Annamese troops in France; and one from New Orleans. The cases were all pure, heavy infections of Pentatrichomonas. There are reports of serious trichomonad diarrhoeas on the Mexican border, in Peru and in Venezuela. These may well be due to Pentatrichomonas rather than to Trichomonas as reported by Escomel and others. It is advisable in diagnosis of these cases to count the flagella. In all these trichomonads there is one flagellum which beats in the rhythm of the undulating membrane while the remainder (3 in *Trichomonas* and 4 in *Pentatrichomonas*) beat independently and at a different rate, so that in attempting to count flagella one must always seek for one more flagellum than you can readily count. Clinicians in the Tropics have an opportunity to settle this matter as to whether or not the trichomonads are really serious infections, and to determine whether or not Pentatrichomonas is pathogenic.

Dr. Seale Harris. — Dr. Hegner's observations and his experiments may be of great value in treatment of flagellate infections. However, I want to sound one note of warning. That is, from the viewpoint of nutrition it may be harmful to feed a strict protein diet, or very high protein diet, over a very considerable period of time. I think that an almost complete protein diet may be given for a few days, or long enough to eliminate the flagellates from the intestines; but I fear that given over a long period of time it might result in serious kidney trouble or other nutritional disturbances.

When an excess of proteins is ingested the liver tries to take care of it, and the end products of imperfectly metabolized proteins are eliminated through the kidneys — and that may cause trouble. Dr. E. V. McCollum told me that when, after feeding rats on a 65% protein diet for a long period of time, he found distinct changes in the kidneys which suggested that a high protein diet might result in permanent kidney damage.

The human body needs about 75 grammes of protein in the 24 hours, and a diet very much in excess of that might give trouble. It should be remembered that 58% of proteins may be burned as carbohydrates, so that to get more than 75 grammes of protein, a diet of 150 or 200 grammes of proteins might be given without any harmful results. If we eliminate the carbohydrates, the inclination would be to make up the number of calories by means of fats. An excess of fats is liable to lead to acidosis, and it seems to me that when a person is placed on a high-protein, high-fat diet, it should be a routine matter to examine the urine daily for diacetic acid and acetones. Fat produces this acidosis and fats burn in the fire of the carbohydrates. Therefore, unless carbohydrates are given with fats, acidosis may occur. That is a problem in diabetes, the acidosis bringing on coma due to failure to eliminate or burn the fatty acids, and in that condition there must be a high carbohydrate diet to burn up the fatty acids.

I merely want to sound this note of warning while appreciating the splendid contribution Dr. Hegner has made. I have observed a number of cases of intestinal flagellates, which are very widespread in the United States, among individuals who have had no diarrhoea; but in other cases a heavy flagellate infection seems to be the cause of severe diarrhoea. In such cases we have found that there is an absence of hydrochloric acid in the stomach, and the use of dilate hydrochloric acid is helpful in the flagellate diarrhoea.

Dr. Charles C. Bass. — I wish to express interest in and appreciation of this very valuable contribution. I think the fact of

the influence of diet upon the intestinal flora rather than upon the fauna is already pretty well established. It is well known that by diet we may change the intestinal flora almost at will. It is interesting that by using a certain kind of diet, such as lactose and detrin, we can establish an aciduric intestinal flora in which the intestinal contents become acid, similar to the reaction of the feces of the normal nursing baby.

The more completely carniverous the diet, the greater the tendency to neutral or alkaline reaction of the intestinal contents. A completely carniverous diet changes the intestinal flora entirely, and there is every reason to think that it might have similar effect on the fauna. It may be, therefore, that the effect of a carniverous diet upon intestinal flagellates reported by Dr. Hegner, results from the change that occurs in the reaction of the intestinal contents.

Dr. R. B. Nutter. — I have been interested in Dr. Hegner's experiments at Tela from the clinical side. In vaginal smears from 20 patients, flagellates were demonstrated in 50%. I observed that the parasites were found in patients with vaginal discharge. In 2 instances of positive findings, the vagina was sterilized with 3% iodine for operation, and 4 days after operation there seemed to be no diminution of flagellates. I have also observed that flagellates increase in dysentery patients when on milk diet.

Col. Bailey K. Ashford. — I wish to record that while we often found Balantidium coli in 3,914 examinations of faeces in as many cases in Utuado in 1913, there were nevertheless only two which we noted as having a true Balantidic dysentery. I also had a case of long-standing and severe lamblia diarrhoea in a naval surgeon, which a carbohydrate and sugar-free diet and all remedies were unsuccessful in modifying.

I take this occasion of referring to Dr. Connor's interpretation of what I said concerning bacillary dysentery in Porto Rico. I think that I made it clear that bacillary dysentery had been endemic on the island, but that as a result of the hookworm campaign and on account of sanitary measures taken of a general character, I had been unable to find it recently. I only meant to say that it was in apparent abeyance at the present time, not that either amebic or bacillary dysentery did not exist in Porto Rico.

Dr. W. E. Deeks. — As Dr. James and a number of others can testify, it was exceedingly common to find in the stools of the native population admitted to the hospital a series of ciliates and flagellates. Unfortunately, we did not have a protozoölogist who could determine the exact classification. At any rate, they were

exceedingly numerous and from my clinical experience I failed to satisfy myself that any of these organisms caused diarrhoea or dysentery. Now I may be absolutely wrong in this because we have in the Tropics — and I have had referred to me in New York — a series of patients who suffer from chronic diarrhoea and frequently associated with it some of these organisms.

I know that practically all the cases that I come in contact with are the victims of an unbalanced diet. If you correct the patient's diet he gets well. They may still have flagellates, but in patients in the Tropics who live on an excessive amount of carbohydrates, and particularly when associated with excessive amounts of cane sugar, we are bound to have a series of digestive and bowel troubles without the presence of ciliates or flagellates. I have not recommended a protein diet, but a properly balanced diet. I mean by this that I give a man a normal amount of meat, limit his carbohydrates to say from 5 to 6 slices of (preferably) whole wheat bread a day (or its equivalent in other forms of carbohydrates) and all the green vegetables and fresh fruit he desires in order to satisfy his appetite. In the course of a few days you will find that these cases of diarrhoea will practically clear up without anything else.

The only drug I use is dilute nitric acid in 15 drop doses administered in a tumbler of water, with ½ a drachm of essence of pepsin, before meals. I do not know what physiological or chemical action takes place, but I do know the patients get well. There are a number of men who have had clinical experiences similar to mine, and can give similar evidence. I regret to say that I have never been able to incriminate flagellates or ciliates as the cause of diarrhoea unless in association with the use of unbalanced diets.

Dr. Robert W. Hegner (*Closing the Discussion of His Own Paper*). — Both Dr. Kofoid and Dr. Nutter have mentioned a milk diet with respect to these intestinal flagellates. Dr. Magath, of the Mayo Clinic, told me that when patients with flagellate diarrhoea came into that clinic they usually were put on a milk diet. They always got worse and then were sent home. I tried a milk diet on rats and it did not seem to cause any decrease in the number of flagellates. That, I believe, is similar to the experience that Dr. Nutter had with his patients. There may be a difference between young and old rats. Perhaps if the rats are not infected it is impossible to infect them if they are kept on a milk diet, but I do not believe a milk diet is satisfactory in clearing the intestinal tract of the flagellates.

As Dr. Kofoid suggested, changes in the hydrogen ion concentration is one of the first factors that one thinks of as the cause of the disappearance of these flagellates. I took some readings of

both the experimental and the control rats, but did not find a sufficient difference — it seemed to me — to account for the disappearance of the flagellates, as the difference in the readings was not as great as the difference in readings of cultures in which these flagellates were being cultivated. I am not sure whether Pentatrichomonas occurs at Tela or not. I have made slides of a number of the specimens obtained there, but they have not been stained yet, and it will remain for future work to determine that point.

Regarding the danger from a meat diet — I may say I know almost nothing at all about nutrition. The diet that I am suggesting was made out for me by Dr. McCollum and Miss Simmonds, and it is advocated that it be used for only a week or two, and then discontinued for a time, and then taken up again. I do not believe that treatment will cause any damage.

As I suggested in my paper, and as Dr. Bass states, the intestinal flora is very easily changed within 4 or 5 days. In a rat that is ordinarily fed on a carbohydrate diet the bacterial content changes from 99 of the acidophilous type of bacteria to one of the putrefactive type, to 99 of the putrefactive type to one of the acidophilus type, and I think it is this great change in the bacterial content that accounts for the disappearance of the flagellates that live in the lower bowel. This problem was undertaken, not in order to find some means of decreasing the number of flagellates or curing flagellate diarrhoea; it was undertaken with the idea of determining what effect changes in the environment in the intestine would have upon the protozoa living in the intestinal tract — a special biological problem.

Dr. Deeks brought up the question of pathogenicity. One of the results of this work, if it is carried out further by physicians who have control of patients over a long period, I think will be a decision with respect to whether the flagellates are present in abundance in the intestine because there is an intestinal disturbance which is favorable for their growth and multiplication, or whether that disturbance is due to the presence of the flagellates. I do not hold that there is any such thing as flagellate diarrhoea. I do not know whether these flagellates cause any intestinal disturbance. My work so far indicates that the flagellates do cause intestinal disturbance, but this has not been proved.

Dr. James mentioned the small percentage of lamblia in the Canal Zone. I found the same to be true in Tela. Instead of an average of about 12% I found only 3 or 4% — I do not know just how many, but very few cases of lamblia.

A CLINICAL AND BACTERIOLOGICAL ANALYSIS OF THE BACILLARY DYSENTERY CASES IN ANCON HOSPITAL DURING THE PAST FIVE YEARS

Roland C. Connor, M.D., and Lewis B. Bates, M.D.

Bacillary dysentery is endemic in all parts of the civilized world and, strictly speaking, is not a tropical disease. Its relatively more frequent occurrence in the tropical and subtropical zones gives it an important place in the study of tropical diseases, and in the discussion of health problems in the Tropics. Situated as we are, on the Isthmus of Panama and among the same class of people as are in the neighborhood of the hospitals of the United Fruit Company, it occurred to us that a resumé of the cases of bacillary dysentery treated in Ancon Hospital during the past 5 years might be of interest, especially to the superintendents and members of the staffs of the United Fruit Company hospitals. Medical literature offers little on the prevalence of this disease in tropical America.

It has been shown that the disease occurs more frequently in localities where sanitation is defective. Since the Canal Zone and the adjacent cities of Panama and Colon are directly under the strict supervision of the Health Department of The Panama Canal, lack of sanitation as a causative or contributory factor in this locality can be practically eliminated. This applies especially regarding the water supply, sewage disposal, and flies. The milk supply for the Canal Zone has been pasteurized during the whole of the 5-year period under consideration, and the supply for Colon and Panama has been pasteurized during most of that time. The spread of bacillary dysentery on the Zone and in the adjacent cities, we believe to be wholly due to carriers.

Our first outbreak occurred in May, 1918, among the nurses at Ancon Hospital. At the time, 60 nurses were taking their meals at the hospital mess. During 1 week 10 were ill with bacillary dysentery due to *B. dysenteriae*, Group II; 3 of the cases were rather severe, the others mild.

Efforts were promptly made to locate the source of the infection. Stool cultures were made from all members of the nursing staff, waiters, food-handlers and kitchen help. The carrier was found.

He was a Panamanian who lived in the city of Panama, but during the day was employed as a waiter at the Ancon Hospital mess. He waited on the table where 7 of the nurses who contracted the dysentery took their meals. This man was sent for, and a careful inquiry into his past history was made. He was asked whether he had had diarrhoea or dysentery recently, and stated that he had not, but that on the contrary he was habitually constipated. His condition was explained to him, and he was given an admission slip to enter the Hospital. However, he did not enter the Hospital, never showed up for treatment, never returned to work, forfeited the pay due him, and could not be found again, although the Health Officer of Panama made every effort to locate him.

Following this outbreak, we paid more attention to the dysenteries and diarrhoeas admitted to the hospital. Ward physicians were instructed to view with suspicion all cases of gastro-intestinal upset, especially in the children's wards, and to have the stools from all such cases cultured for *B. dysenteriae*. In addition, the nurses were required to note on every chart in the children's wards the character of the stools. Thus a double watch was kept for dysentery infections so as to prevent any possible outbreak of the disease among the hospital patients. The maids and attendants in these wards are all negro women, above the average in intelligence, and under the direct supervision of the nurses. The latter are all graduate nurses employed in the United States.

There had been sporadic cases of bacillary dysentery in Ancon Hospital for years, but previous to 1918 at no time had routine stool cultures been made on all cases of enteritis and enterocolitis. Since the summer of 1918 all such cases have been cultured. This paper covers the 5-year period from 1919 to 1923, both inclusive. During this period 66 cases of bacillary dysentery were diagnosed and treated in Ancon Hospital, as follows:

1919	9
1920	7
1921	28
1922	6
1923	16

The ages were from 3 months to 59 years. From 3 months to 5 years, inclusive, there were 35 cases; over 5 years, 31 cases. Of the cases, 13 were under 1 year of age.

Of these cases, 45 were black and 21 were white, and 27 of the children under 5 years of age were black — 8 were white American. Residence of cases was as follows: Canal Zone 33, Panama City 22, Colon 8; 3 came from ships plying between the west coast of the United States and South America. The average time spent in the hospital was 15.8 days per patient; the shortest time was 6 hours, and the longest 50 days. The last-named case was an adult who developed multiple arthritis involving the left ankle and knee and both wrists.

There were 19 deaths in the series; 6 occurred within 24 hours after admission, 2 within 48 hours after admission, and 2 within 60 hours after admission. All of the deaths were infants and children under 6 years of age. The ages and number of deaths were as follows: 3 months to 1 year inclusive, 11; over 1 year and under 5 years, 7; and over 5 years, 1. Of the deaths, 2 cases were white children; one was complicated by malnutrition and hydrocephalus, and the other by malnutrition and microcephalus. The other deaths were of negro children, mostly of West Indian parentage. Other complications were the following:

Malnutrition	8
Convulsions	5
Otitis media and sinusitis	5
Arthritis	3
Measles	3
Acute bronchitis	2
Congenital syphilis	1
Acquired syphilis	1
Gangrenous stomatitis, septicaemia and pyemia	1
Congenital debility and premature birth	1

Most of the admissions were during the months of October, November, and December. From January to July, both inclusive, there were 23 cases; from August to December, both inclusive, there were 43 cases. The prevailing opinion that the height of morbidity for diarrhoeal diseases occurs during the beginning of the rainy season, which is in May on the Isthmus and known locally as "Mayo," is not borne out by the records of Ancon Hospital. The average for all cases admitted for diarrhoea, enteritis, enterocolitis, and colitis during this 5-year period was higher in February and March, dry-season months, than in May and June, the first 2 months of the rainy season.

A summary of all the cases treated as diarrhoea, enteritis, enterocolitis, colitis, and dysentery exclusive of amoebic dysentery, in the hospitals of the Canal Zone (Ancon and Colon hospitals), and the hospital of the City of Panama (Santo Tomas Hospital), for the 5-year period from 1919 to 1923, is given in the following table:

Year	Canal Zone Hospitals	Santo Tomas Hospital
1919	104	151
1920	98	184
1921	161	178
1922	119	194
1923	169	155

During this 5-year period no cases of bacillary dysentery were reported in the Annual Report of the Chief Health Officer of the Panama Canal, from Santo Tomas Hospital, City of Panama. Neither were any cases of bacillary dysentery reported by the private physicians in Colon and Panama. Laboratory examinations, in the case of notifiable diseases, are made free of charge at the Board of Health Laboratory of Ancon Hospital, for these physicians. However, practically no advantage has been taken of this arrangement, so far as dysentery is concerned.

In our series of cases, stool cultures were made within 24 hours after admission in 31 cases; within 2 days, in 11; within 3 days, in 6; within 4 days, in 2; and within 5 days, in 2. No cultures were made in 7 cases; 4 of these being admitted in a dying condition, and not living 24 hours after admission. In

42 cases the stool cultures were positive for dysentery bacilli on the first examination; in 11 cases, negative on the first examination; in 3 cases, negative on the first 2 examinations; and in 4 cases, negative on the first 3 examinations.

For the past several years we have classified and designated dysentery bacilli by "Group," as recommended by Thjøtta[1], rather than by the names of individuals: —

Group I. The Shiga type (non mannit-fermenting, toxic type).

Group II. The Flexner, Strong and Y type (mannit-fermenting, atoxic type, pseudo-dysentery bacilli, Sonne's Groups I and II).

Group III. Group III of Sonne (the new member of the mannit-fermenting types).

Group I. — The Shiga organism is well known and practically never confused with any other type of dysentery organism.

Group II. — This group includes a long list of dysentery bacilli which ferment glucose and mannite and various other sugars (except lactose) with the production of acid, and most of which have common group agglutinins. This group includes "Y," Flexner, Strong, and practically all the more commonly described types of dysentery bacilli. These organisms differ among themselves in their effects on the various sugars, and by agglutination in higher dilutions of their own respective agglutinating sera. Sometimes their differences are so slight that it is difficult to say to which type a given organism belongs. These differences seem to have no practical importance, and in many instances are inconstant and unreliable.

Group III. — This organism seems to be entirely distinct from those listed in Groups I and II. Thjøtta[2] describes its colonies as follows:

> The dysentery bacilli of the older types (Shiga, Y, Flexner and Strong types) always produce delicate, sharply-contoured colonies on the plate cultures, of the same appearance as the

[1] THJØTTA, TH. "On the Bacteriology of Dysentery in Norway," *The Journal of Bacteriology*, Vol. IV, page 377, July 1919.

[2] THJØTTA, TH. "On the Bacteriology of Dysentery in Norway," *The Journal of Bacteriology*. Vol. IV, pages 366–367, July 1919.

colonies of the typhoid and paratyphoid bacilli. The new group C (Danish III), however, in this respect differs a good deal from the other groups. This group produces rather large colonies, a little denser than those of the other groups and showing a peculiar crenated irregular edge. The center is usually the densest part of the colony, the peripheral parts getting gradually thinner. Blue colonies of this type growing from a dysentery stool render it very likely that we have to deal with bacilli of this group. There may, however, be seen colonies of other types belonging to this group. Sometimes we find them very small and dense, at other times large and dense with an edge growing out like a bunch of hair. Both of these colonies show irregularities of agglutination, either being inagglutinable or showing spontaneous agglutination in saline solution. If cultivated for some generations on agar, these colonies will as a rule develop colonies of the ordinary type, both as regards agglutination and growth.

This organism ferments glucose and mannite with the production of acid and many of the other sugars, upon prolonged incubation. It produces acid in lactose media after variable periods of incubation. Many of our strains have fermented lactose within 48 hours. It is impossible to make a high titer-agglutinating serum for this organism. It is not agglutinated by any of the other dysentery-agglutinating sera, so far as we know, and its own agglutinating serum has little or no effect on the other dysentery bacilli.

Recovery and Identification of the Dysentery Bacillus. — Flecks of mucus, preferably blood-stained, are spread on Endo plates. These flecks are incubated for from 18 to 24 hours. Suspicious colonies are then picked and inoculated on Russell's double sugar medium (1% lactose and 0.1% glucose). Subcultures and agglutination tests are made from the growth on this medium. Subcultures are made on the following semi-solid media: Glucose, lactose, mannite, saccharose, dulcite, and maltose, also in litmus milk. These are incubated 7 days or longer, and a record of the changes occurring during this time is kept.

NUMBER OF CASES AND DEATHS DUE TO EACH GROUP OF DYSENTERY BACILLI

Organism	Cases	Deaths
Group I. (Shiga)	4	0
Group II. ("Flexner," "Y," "Hiss Russell," etc.)	39	14
Group III. (Group III of Sonne)	18	3
Group not determined	5	2
Total	66	19

Only 4 of our cases were due to the Group I, or the Shiga, organism. These were sporadic cases, did not have the severe bloody flux usually seen in this type of dysentery, and had no fatalities.

The diagnoses made on cases which were not cultured during life, but from which *B. dysenteriae* were recovered at autopsy, were as follows.

Acute undetermined infection	3
Diarrhoea and enteritis	1
Acute enteritis and convulsions	1
Malnutrition and acute nephritis	1
Food poisoning	1

This shows that 10 per cent of the cases would not have been diagnosed, had they not gone to autopsy.

Symptomatology. — A variety of intestinal disorders may be mistaken for bacillary dysentery, and vice versa. It too frequently occurs that in children the disease is overlooked and the symptoms are attributed to errors in diet. A child admitted to the hospital with high fever, convulsions, and diarrhoea should be suspected of having bacillary dysentery, especially if the stools contain mucus and are blood-tinged. In our cases all the children except one had temperatures of from 101° to 104° F. ushering in the infection. Of the adults, 7 had a temperature of 100° F. or less, and 7 had no fever. The appearance of the stool is suggestive, but not diagnostic.

The appearance of the stools in bacillary dysentery, amoebic dysentery, and other intestinal infections is well described in the literature, as is the symptomatology in general, and we shall not dwell on these features. However, we do wish to state, in fact to emphasize, that in infants and children residing in the Tropics all cases ordinarily diagnosed as enteritis or enterocolitis should be regarded as bacillary-dysentery suspects. It is impossible to differentiate between them clinically. The attempt should be made to rule out, by physical and ward-laboratory examinations, such intestinal infections as *Entamoeba histolytica* and *Schistosoma mansoni*, also the Balantidium and the flagellate diarrhoeas. In adults, rectal examination should be made for syphilis, cancer of the rectum, and internal and ulcerative haemorrhoids. In infants, intussusception should be ruled out. Tuberculosis of the bowel should be considered in the chronic types of enteritis or colitis.

The acute fulminating type of bacillary dysentery is usually ushered in by chill, fever, vomiting, and dysenteric symptoms; shows acute toxaemia; and is easily mistaken for food poisoning. The clinician will avoid many pitfalls, and much humiliation in the autopsy room, by suspecting bacillary dysentery in such cases and taking early precautions to prevent its spread while waiting for stool-culture reports. Fresh stools should repeatedly be sent to the laboratory for culture. The selection of material should be made by the ward physician or the bacteriologist, and not left to the judgment of a nurse or a hospital attendant. Neither should the microscopical examination of a stool from a suspect dysentery case be left to an inexperienced microscopist or technician. *Amoeba coli* is often mistaken by the inexperienced for *Entamoeba hystolitica* and so reported, so that the patient is subjected to emetine treatment on a false diagnosis. In most hospitals, and in private practice where a bacteriological laboratory is available, this work is too often neglected, or carried out in an indifferent manner.

In our experience at Ancon Hospital it has been very difficult to impress upon the ward physicians, especially in recent years because of the frequent transfers of the staff, the importance of viewing with suspicion all cases of acute gastro-intestinal upsets, especially those cases with blood and

mucus in the stools. Nurses in the children's wards have been instructed to note on the chart of every patient, daily, the gross appearance and character of the stools passed. These instructions are carried out consistently only when the physician in charge of the ward sees that the nurses' notes in this respect are complete.

To have this done seems easy, but as a matter of fact the average physician is not thinking of bacillary dysentery, especially in relation to infants and children. Many times when he is asked what the gross appearance of a child's stool is he cannot tell, even though the chart may show 4 or more stools per day. In the microscopical examination of the stool of an infant he is apt to be looking for intestinal parasites or ova, with little or no thought of the appearance of a bacillary-dysentery stool. Dysenteric symptoms in a child he often attributes to a gastro-intestinal upset from bad feeding. It is only after the preliminary dose of castor oil and the lapse of two or three days without improvement, that he has the stool cultured for the dysentery bacillus, and then one negative report is too often considered sufficient evidence to rule out dysentery. One negative report means nothing. A stool specimen should be sent to the laboratory twice daily for at least 3 days. The physician should not wait for a report on the first specimen before submitting others.

Children are more susceptible to bacillary dysentery than adults and it is more often fatal with them, or at least that is true of the class of children we admit to Ancon Hospital. It is also more difficult to prevent cross infection in children's wards. Despite all the precautions that we have used, especially in the children's wards, 7 of our cases apparently developed in the ward, and 5 of the 7 died. The high death rate in this instance was undoubtedly due to the low resistance of these children, as they were either malnutrition cases or convalescents from acute illness. In some cases it was simply a terminal infection. Lowered resistance due to constitutional disease and undernourishment leaves a child an easy prey for the dysentery bacillus.

As stated, autopsies have shown that 10 per cent of our cases were undiagnosed during life. These cases were infants and children on whom we thought we were keeping a

close check. When the number of cases of enteritis, enterocolitis, and colitis that were so diagnosed with only one negative stool culture is considered, and in addition the number of possible *B. dysenteriae* cases which were admitted too late in the disease to have cultures made, it appears safe to assume that far more than 10 per cent, perhaps 20 per cent of such cases had the dysentery bacillus as a primary or secondary infecting agent.

We stated at the beginning that we believe that carriers are entirely responsible for the spread of the disease in the Canal Zone and in the adjacent cities of Colon and Panama. The sanitation of the Canal Zone and terminal cities is closely supervised, and they are models of cleanliness for any locality. The outbreak among our nurses was traced to a healthy carrier who gave no history of a recent illness. As carriers of the dysentery bacillus or the carriers which are detected are much rarer than are the carriers of the typhoid bacillus, we desire to make mention of one other and more recent case of which we have personal knowledge: —

This man, a soldier, was admitted to Ancon Hospital as a carrier of *B. dysenteriae*, Group II, on October 10, 1923, and transferred to the Walter Reed General Hospital, in Washington, on December 11, 1923, at which time his stool cultures were still positive for the dysentery bacillus. His first attack of dysentery was in January, 1923. No cultures were made in the Post Hospital at that time. In August, 1923, he had dysentery again and stool cultures at this time were positive for *B. dysenteriae*, Group II. This man was a carrier certainly for 4 months, and probably from the time of his first attack of dysentery in January. Singer[1] states that in the Hagenau epidemic in the German army in 1915, 139 healthy carriers were found along with the 232 sick, and that 13 of the carriers were known to harbor the bacilli from 137 to 404 days. He also states that the Flexner carriers were too numerous to detain. While the convalescent carrier is undoubtedly the common factor in the transmission of bacillary dysentery, we do not believe (as some authors have stated) that the healthy carrier is a negligible factor.

[1] SINGER, G. "Dysentery Among the Troops, "*München. med. Wchnschr.*, February 9, LXII, No. 6, pages 177–216, as abstracted in the *Journ. Am. Med. Assn.*, Vol. LXIV, page 1,115, Mar. 27, 1915.

Our treatment in this series of cases was for the most part symptomatic. All suspects were isolated in the ward away from the other patients, and the beds were tagged "Dysentery precautions." This safeguard was continued until at least 3 negative stool-cultures were obtained. Saline laxatives were given in small doses for 2 or 3 days, followed by large doses of bismuth subnitrate. A liquid diet consisting of soups, broth, consommé, milk diluted with barley-water, and albumen water, was given the adults. Milk and barley-water, and later acidulated milk (usually acidulated with hydrochloric acid) and orange juice were given infants and children under 2 years of age. Saline irrigations of the lower bowel were given once or twice daily. Serum treatment, with the polyvalent anti-dysenteric serum, was used a few times but usually too late or in hopeless malnutrition cases with a complicating *B. dysenteriae* infection. No benefit was noted in the cases in which it was used. The mild cases do not require it, and it is useless in the advanced malnutrition cases of infants with bacillary dysentery as a terminal infection. The delay in awaiting the result of a stool culture in suspect cases, is valuable time lost if serum treatment is contemplated. During an epidemic this delay is not necessary. But in the absence of an epidemic, the cases of non-specific enterocolitis so far outnumber the dysentery cases that the serum treatment is not warranted until a positive diagnosis has been made.

CONCLUSIONS

1. Bacillary dysentery is a common disease on the Isthmus of Panama, and the mortality is high in infants and children under 5 years of age.

2. Group II (Flexner, Strong, Hiss Russell, Y etc.) and Group III of Sonne are the common types of dysentery bacilli in this locality. Group I (Shiga) is comparatively rare.

3. In hospitals extreme care must be used, and strict rules observed, to prevent the spread of the disease to other patients. Even then an occasional case will develop in the ward.

4. Even in mild epidemics, a search for carriers should be made at once. Any found should be prevented from handling food and drink in any way, shape, or manner.

5. During a 5-year period, at least 10% of the bacillary-dysentery cases in Ancon Hospital were wrongly diagnosed, as shown by autopsy. Probably a larger percentage of the diarrhoeal cases which were discharged had a wrong diagnosis.

6. The positive diagnosis of bacillary dysentery is made by the laboratory. An early tentative diagnosis should be made by the attending physician, and dysentery precautions should be ordered at once.

7. Many physicians in the Tropics do not seem to be aware of the frequency and seriousness of bacillary dysentery, especially in infants and children. We believe that the disease is not given the attention in tropical America which its frequent occurrence merits.

DISCUSSION

Dr. H. C. Clark (Opening the Discussion). — I have not had much experience with bacillary dysentery except at autopsy. Most of my cases in the Canal Zone occurred in children, and in the majority of the cases the disease seemed to develop as a terminal feature in that group of infants spoken of as malnutrition patients. It is not always easy to get a positive culture. Apparently most cases come in after the disease has become a badly mixed infection and is producing abundant exudate. I know that the laboratory always wants a half-dozen chances at specimens before it is willing to render a negative report. This is true at autopsy where we have learned that the best prospect for a positive culture is gained by cleaning off the mucosa, and even some of its exudate, before we select material for culture. Bacillary dysentery has never been a serious epidemic disease in Panama nor, thus far, in our location at Honduras. Sporadic cases are occasionally found throughout the year. Only two of the Shiga type have been observed at Tela during the last year.

Dr. R. B. Nutter. — Two years ago in Honduras we had the epidemic of bacillary dysentery to which Dr. Clark refers, and about half of the laborers in one district were incapacitated. We had no facilities for cultures at that time. The epidemic spread very rapidly but was easily controlled by sending all the patients with diarrhoea to the hospital, and having camp police to enforce the use of latrines. That was the only important epidemic in our division.

Dr. William H. Park. — Back in 1902 we had the only large epidemic of dysentery in the region of New York that I know of. There were within 6 weeks some 1,500 cases in the villages just

north of the city, not actually in the city. These cases were etiologically about equally divided between the Shiga and the Park-Hiss, or Y, type and many were due to both types; the cases were almost equally severe whether they were due to one or the other of the types. At the time of this epidemic, the City was enlarging Riker's Island by filling in with garbage, and had a large group of laborers there. One laborer developed a mild dysentery of the Flexner type and since he was unable to do the hard work, they put him in the kitchen. In about 10 days nearly all of these laborers had come down with severe dysentery. The discharges showed abundant bacilli of the Flexner type.

It seems to me, from the above instances alone, it is evidently a mistake to speak of the Shiga type giving rise to the toxic form of dysentery and the Flexner, Park, Strong, etc., types as causing the non-toxic form. The Shiga bacillus on the average gives rise to the most toxic cases, but no one who saw the cases just mentioned would call them non-toxic. The symptoms in the outbreaks alluded to were just as severe in the cases due to the paradysentery types as in those due to the Shiga type. I think the suggestion to get away from names for these types is a laudable one, but I do not like the name pseudodysentery bacilli. I prefer to call these paradysentery strains.

As to the making of cultures, we found very useful a small rectal tube with an opening on the side. After a cleansing douche is given, the tube is passed up into the bowel and a culture made by rubbing a swab against the mucous membrane pressed into the tube opening. In this way often an almost pure culture could be obtained. I am not quite sure whether I heard Dr. Connor correctly when I thought he suggested that in the Tropics we should go about making cultures of healthy people to detect carriers of dysentery and paradysentery bacilli. I don't know of any northern city where we make cultures for dysentery bacilli, without first getting traces of mucus and blood.

In New York City, where we have practically no dysentery of children, the paradysentery types can nevertheless occasionally be detected in their discharges. I would not want to go about among little children making cultures and isolating the positive cases. In the Tropics it may be different. I wonder how many of these cases of dysentery-carriers which later became severe were found by cultures. Does Dr. Connor think it right to call a case dysentery simply because we find the dysentery bacillus? You might as well call a healthy child a case of tonsillitis or pneumonia if you found in the throat the streptococcus or the pneumococcus.

If you hunt in chronic intestinal cases for one of the para-

dysentery bacilli or even the Shiga bacillus in infected territory, of course you will occasionally find them in cases in which you would not expect to. It is not fair to call these cases of dysentery. I wonder whether the hospital releases all cases only on a number of negative cultures. I believe in having these examinations made in all hospital cases, but the information obtained should be utilized with great care. I doubt whether a health department should make cultures regularly of healthy people, with the exception of food-carriers.

Dr. Aldo Castellani. — I should like to be permitted to say a few words on three points connected with the very interesting communication on dysentery which we have listened to today: (1) The so-called "Sonne bacillus," (2) the presence in certain cases of bacterial dysentery of a nosoparasite which has nothing to do with the etiology of the malady, and (3) the treatment of bacillary dysentery by means of rhubarb.

1. *Sonne bacillus.* — The characteristics of this bacillus are that it ferments, when it is recently isolated from the stools, lactose in addition to other sugars, and is fairly toxic to the rabbit. It seems to me that this germ is identical or very similar to *Bacillus metadysentericus*, which was first isolated by me in 1911, and again in 1915, in cases of dysentery in patients coming from Albania, and also in certain cases at Taranto. The characteristics of *Bacillus metadysentericus* are just the same as those of the Sonne bacillus — that is to say, it produces fermentation (with no production of gas) in lactose when recently isolated, and, as shown by Professor Olivi and others, it is fairly toxic to the rabbit and is not agglutinated by Shiga, Flexner, or other sera. If the two organisms should be identical, according to the rules of nomenclature the correct name would be *B. metadysentericus*.

2. *A nosoparasite often found in bacillary dysentery.* — This is a most peculiar germ. The colonies on colored media are identical with the colonies of the true dysentery bacilli. For instance, on MacKonehe's medium the colonies are white. This germ is most polymorphic. It may develop under 3 principal types: the bacillus; the comma or Vibrio type; and finally the spirochaetic type, long spiral forms being present. At first I thought I was dealing with 2 or 3 germs which were living or growing together, but by plating and replating I came to the conclusion that it was the same germ which at times produces bacillary forms, at other times Vibrio and long spirillar forms. I called this germ Vibriothric zeylanica. I shall be pleased to supply cultures of it to any medical man who might be interested.

3. *The rhubarb treatment.* — When I was in Ceylon and I had

cases of bacillary dysentery in children, and could not get the dysentery serum, my line of treatment was practically always the same: I used to give a mixture of rhubarb the formula of which is:

Pulv. Rhu. Co ℥ss (in certain cases ℥i)
Ag Chlorof. ad ℥i.

Shake the bottle, and give one teaspoonful every 2 hours, to a child 2 years of age. It was most interesting to see how quickly the symptoms of dysentery disappeared. Unfortunately the same treatment in adults did not succeed and therefore I never published the method, though I occasionally referred to it in discussions on intestinal conditions, at the meetings of the local branch of the British Medical Association. Recently the method has been rediscovered in British East Africa and several medical men there have apparently obtained good results also in adults.

Dr. Henry Rose Carter. — In the handling of the sanitation around camps during the late war, one of our most difficult stations was Newport News. Roughly, I judge 500,000 to 550,000 troops were shipped from there. The camps were not so large themselves — but it was a port of embarkation. At this place, which includes Newport News, Hampton, North Newport News, and another town, whoever was concerned with the preparation of food at restaurant, boarding house or hotel, was examined to see whether he was a carrier of typhoid or dysentery. As I recall, we found a fair number of such carriers — possibly as many as 7.

We had no authority to prevent their employment, but we had authority to paste a card on the house stating that no man in uniform was allowed to take his meals there on account of the presence of a carrier of dysentery or typhoid, as might be the case. The warning, of course, was also a safeguard to the rest of the public. What we prevented I do not know. The town was simply a place for passing through, and if any soldier should contract dysentery or other disease from these carriers he would be aboard ship and we should not know about it. The results therefore were not determined. We required 3 negative examinations (only 2 of which could take place in the same week) before any one could be employed, without causing the posting of a warning card, for handling food.

Dr. H. J. Nichols. — I wish to congratulate Dr. Connor and Dr. Bates on this important paper, because I think that bacillary dysentery is much more widespread and more important than we realize. For example, I know that in the United States Army in the last year we have had outbreaks in almost all of our geographical divisions. The country is divided up into 9 areas and in each of these we have a large laboratory; from almost all of them we

received at the Army Medical School during the past year transfers of cultures from cases of bacillary dysentery which occurred either sporadically or in epidemics, mostly of the Flexner type.

The same is true in the Philippines. In fact, I think at the present date the problem of bacillary dysentery is the principal one in the Philippines and over there, in the way of diagnosis, I believe they have developed the cytological method — the examination of the cells of the stools — as a rapid diagnosis. I have had no experience, but I know that Dr. Houghout of the Philippine Bureau of Science and also our own men think it is a very reliable way of arriving at an early diagnosis which would make the possibility of serum treatment more prompt.

In this connection I should like to emphasize the desirability of examining the gall bladder at autopsy or the duodenal contents during life as a possible site of the carrier lesion. This method is well known in typhoid and cholera, it is possible in amoebic dysentery, and deserves more consideration in bacillary dysentery. In regard to the examination of healthy persons, I think we should at least go as far as to examine the food-handlers. If the servant referred to had been examined before being assigned to the kitchen, the disease might have been discovered. To enforce examination of food-handlers is difficult, for if the housewife can get a good servant, that is all she is interested in, but I believe medical officers should examine servants for bacillary dysentery, amoebic dysentery, skin diseases, etc. It is the only way I can see whereby we can make any advance in handling the situation. One epidemic that I saw at the docks of New York, last year, developed in this way — from the kitchen. There was a case of bacillary dysentery among the dockhands. A great many flies were about the place. The kitchen on the boat was not screened and the flies were over everything. Out of a crew of about 20 men on the small boat, there were 13 cases of bacillary dysentery, some of them very mild but some very definite, and the stool cultures revealed the organism. I feel this is a very important subject.

Dr. Milton J. Rosenau. — We have comparatively little bacillary dysentery in New England. Outside of infantile diarrhoea, bacillary dysentery is mainly an institutional affair in our climate. It is preventable and controllable. Of course, this includes the problem of infants. During the World War we examined over 4,000 specimens of feces from healthy male adults, and, regarding the carrier problem, I may say that in this particular study of over 4,000 specimens we failed to find any one of the dysentery bacilli.

Dr. William H. Park. — The use of serum in treatment has been alluded to. We all agree that unless a serum is potent for the

strain causing the attack, it is useless. What it is necessary to remember is that the manufacturer has a habit of putting "polyvalent" on a serum without saying what strains it is potent for. It generally means that it is highly potent for 1 strain or 2 strains, and nothing more. We must therefore know the type of organism we are dealing with in the cases, and what antibodies are present in the serum. If I remember aright, the Asia Minor type of dysentery bacillus was quite different from any of those met with in Europe and America. We should also have serum for the endemic types stored in advance. This can be kept in the icebox for a year if necessary. It obviously cannot be imported from a distance without delay, and there may even be no potent serum anywhere in stock.

The manufacturer should be compelled to put on the vial for what types of bacilli there are potent antibodies. The physician must know what type or types of bacilli he is dealing with if he is to use a serum intelligently.

Dr. Paul W. Wilson. — It may be of interest to know of the epidemic in Haiti which has taken such a large toll of life during the last 2 years, in view of the fact that much Haitian labor goes to other ports. This dysentery, according to the opinion of Dr. Lane and Dr. Bennett, has been endemic there a great number of years, and only in the last 2 years has it taken on a more toxic form. It was a peculiarity, when it did become toxic, that many of the patients had an almost exact clinical picture of cholera and died within 72 hours. It may be of interest to medical officers in other ports to know that many of these Haitian emigrants may be carriers of bacillary dysentery.

Dr. Roland C. Connor (*Closing the Discussion of His Own Paper*). — Our answer to Dr. Park's inquiry as to whether the cases were discharged without our previously examining and seeing that they had negative stool-cultures is, that they were discharged only after 3 negative stool-cultures were taken, on 2 separate days — the best we can do under the circumstances. We cannot keep in the hospital for too long a time patients recovering after mild infection. Formerly we followed the old rule of 3 cultures, 3 days apart — which meant 9 days awaiting negative stool-cultures. In regard to the routine stool-cultures in the hospital in diarrhoeal diseases, especially in the children's wards, I believe that to be a good precaution. As Dr. Park states, in hospitals it is probably all right, but in private practice it is impracticable.

What we are trying to do in this paper is to get the doctor to think in terms of bacillary dysentery, whenever he has to deal with a gastro-intestinal upset, especially in children. If one is called to

see such a case in a child or an adult, let him call for a specimen of stool and see it himself. That is the only safe way. He must know that he cannot depend on the mothers or nurses or any one else, unless it be an experienced doctor to select a suspicious dysenteric stool. It is a fact that some of the cases on our records did not show pus and blood in the stools. These cases died of other diseases on which bacillary dysentery was engrafted, but such patients might be carriers. In hospitals, view with suspicion diarrhoeas, especially those with blood and mucus, but in any case think of bacillary dysentery and be ready to deal with it as soon as possible.

As to Major Nichols' question, food handlers are examined when employed, but at what intervals after employment I am not able to say. I am afraid we are in the same position as others. The employer takes for granted that all is well and thinks the first examination is sufficient, until the employe gets sick. Obviously examinations should be made at intervals of, say, 3 or 4 months, especially in places like Ancon Hospital where there is every facility for making these laboratory examinations.

I was glad to hear Dr. Castellani's suggestion regarding treatment with rhubarb. I shall not forget it, and shall probably have opportunity to put it in use, especially with children.

I was surprised to hear Colonel Ashford say that in Porto Rico there is no bacillary dysentery. Probably there is not much dysentery there, but it is worth thinking about, and it is very improbable that it does not occur to some extent. It would be interesting to know to what extent gastro-intestinal diseases occur in Porto Rico. One of my cases was in a Porto Rican soldier's child — I cannot say where he contracted the disease, as the only obligation which rests on the hospital clinician is to report the case to the principal health office, and he has his chief inspector make a report on the possible sources of the infection.

The question arises, What can we do to keep down the infection? As shown by our records in Ancon Hospital for 5 years, we had several cases due to ward infection despite the fact that there has been fairly close supervision. Any case of gastro-intestinal upset occurring in cases, especially infants and children, in the hospital under treatment for other than diarrhoeal disease, should create suspicion, and you should at once think of bacillary dysentery and take proper measures at once to rule it out.

SOME DATA CONCERNING THE LIFE CYCLE OF THE *SCHISTOSOMA MANSONI*. DISTRIBUTION AND PROPHYLAXIS OF SCHISTOSOMIASIS IN CARACAS

JUAN ITURBE, M.D.

Accurate knowledge of the life history of the different human blood-flukes has always been a matter of the greatest interest to the biologist, and, above all, that part of the life cycle which corresponds to the larval state — that is, the time during which, already enjoying a separate existence, they pass from the intermediate organism to the definite host.

In certain types specifically differentiated, the parasitic life continues in an unbroken succession from host to host, as is the case with the protozoa transmitted by means of an hematophagous insect. As for the trematodes, these parasites adopt during their embryonic state a free aquatic existence, which it is useful to know, provided this period of their lives gives the hygienist an opportunity to hinder the development of the parasite, and thus to save man and animals from infection.

Miyairi and Suzuki (1913–14), Leiper and Atkinson (1915–16) Iturbe and Gonzalez (1916–17–18), Lutz (1917–19), obtained for the first time an accurate knowledge of the life history of the different classes of human Schistosomes, from the time of the penetration of the miracidium into the mollusc host, until the production of the cercaria, a free state of these worms, during which they succeed in infecting man and animals through the skin.

Up to the time of the publication of our work (1916–18) nothing had as yet been written in Venezuela on the larval phase of the life of the trematodes. Observations collected by us from that time to this, enable us to give the experimental results obtained concerning certain details of the life cycle of the *Schistosoma mansoni*, and the distribution and prophylaxis of Schistosomiasis in the valley of Caracas.

When we started on our search for the intermediate host of the *Schistosoma mansoni*, in Caracas, we collected the mollusca that were commonest in valleys: *Ampullaria luteostoma* Swains, *Physa rivalis* Maton, *Planorbis cultratus* Orb, and the *Planorbis guadelupensis* Sowerby. Specimens of these molluscs were put into vessels containing water infected with a large quantity of miracidia of the *Schistosoma mansoni*. Although we were able to observe the penetration of some miracidia into the *Planorbis cultratus*, the evolution up to the appearance of the typical larvae was observed in a constant manner only in the specimens of the *Planorbis guadelupensis* submitted to contamination. The intermediate mollusc host of the *Schistosoma mansoni*, in Venezuela, is a freshwater snail of the class *Gastropod aquatilia*, genus *Limnaecae*. It has 6 spirals, and measures, in its adult state, 24 mm.wide, by 7 mm. high. Its distal extremity is not prominent. When examined from its upper surface, a gradual dip of the spiral is noticeable, forming a conical depression; its undersurface is less depressed. Its teeth are regularly placed, and they have filiform tentacles.

The well-developed examples resemble somewhat the *Planorbis cumingianus*, Dunker, and the *Planorbis olivaceus* Spix, both indigenous to Brazil — from which they differ in their smaller size and the flattening of the last spiral. The colour of the adult specimens collected by us in the irrigation canals around Caracas, is of a yellowish brown. The young specimens differ from the *Planorbis bahiensis*, Dunker, in that their last spiral is more convex; for which reason the upper portion has the appearance of being more depressed; this convexity gives one the impression that it has an upper lip when it reflects light. The degree of inclination of this snail, seen from in front, varies considerably according to the specimens; but it generally has an outward tendency.

The eggs of the *Planorbis guadelupensis* are of a clear yellow colour; they cannot long resist desiccation, and one may easily see them in agglomerations of from 20 to 30 adhering to the upper surface of the mollusc, by means of a glutinous substance. The eggs may also be found on stones and leaves. This mollusc lives in quiet water: at the bottom of wells and canals. It is also found in great numbers in water containing *Nasturtium officinale*, which is its favourite food.

We think this a suitable occasion to give a few details in regard to the evolution of the *Schistosoma mansoni*, which may be of some help in the sanitary campaign against that infection.

The eggs of the *Schistosoma mansoni* are laid by the female, whose ovary is situated in the anterior portion of its body, in the fork formed by the two branches of the intestinal canal. The covering of the egg with its lateral spine is very tough and resistant, and its inner surface is covered with a viteline membrane so very strong that even if the shell be broken, it may continue to cover the miracidium, intact.

The cephalic glands of the miracidium of the *Schistosoma mansoni* are much broader than those of the other two species of human Schistosomes. These organs are unicellular, with large nuclei, and the position of their ducts, and their resemblance to the cephalic glands of the cercariae of Schistosomes indicates that their secretions favour the penetration of the miracidium into the mollusc host.

The miracidium possesses four flame cells whose function consists in draining the anterior and posterior regions of the body.

The flame cells differ from the corresponding cells of the other human Schistosomes in that they are situated perpendicular to the principal axis of the miracidium.

The miracidium of the *Schistosoma mansoni* easily penetrates the tissues of the head or the gill filaments of the *Planorbis guadelupensis*, perhaps owing to the fact that the mucosa of the mollusc has an elective affinity with it.

All the cercariae which penetrate into the mollusc, by either route, succeed in attaining full growth; those which penetrate the gill however, arrive first at the intrahepatic spaces.

The transformation of the miracidium into a sporocyst takes place on the 7th day, at which time its cephalic glands disappear. After 3 weeks the sporocyst contains germ globules of the second generation, and 7 or 8 weeks following the experimental infection, the cercariae already exist in complete maturity.

The larva of the *Schistosoma mansoni* dies in a temperature of from 48 to 50 degrees, and sunlight diminishes its activity. Under experimental laboratory conditions, it lasts hardly

more than 24 hours, and is rarely inactive. When observed under a microscope of from 15 to 20 diameters, it is seen to be 1 or 2 centimetres below the surface of the water and with its tail always pointing upwards. The rapid movement impressed upon this in a lateral direction, as well as the contraction of the body, gives the cercaria a surprising facility of natation.

When examined under a microscope, its movements are characteristic: The muscular ring of the acetabulum is folded over the surface of the slide, while the body diminishes to ⅓ its former size. The tail lengthens considerably, and its 2 bifurcations point outwards, by which means the cercaria is able to change its position with the greatest facility. We have never observed any encysted forms, either in its evolution in the Planorbis or in its aquatic existence.

The anterior portion of the body of the cercaria affects a cylindrical form, tapering gradually up to the oral orifice, which is longer than the acetabulum. There is no sign of a digestive tube or of a pharynx, — only a blind cavity being visible at the bottom of the mouth, which is probably the beginning of the digestive tube. The head of the larva is surrounded by a crown of from 6 to 10 points, which serve to penetrate the skin of the mammal.

The posterior portion of the body contains a ventral orifice and 3 pairs of poison glands. These are rounded before the cercaria is yet mature, but when the cercaria is full-grown they are elongated and placed on both sides of the distal extremity of the body. Its secretion ducts run along the outer edge of the excretory system and disembogue into the anterior portion of the body in the same oral orifice. Each meatus ends in 2 or 3 spines, visible with 800 diameters. Upon the medial line of the body, before the acetabulum, there is a kidney-formed cellular agglomeration of a brown colour, from which starts a small channel ending in the buccal cavity itself. The germ cells occupy a space comprised between the posterior portion of the ventral orifice and the root of the tail.

Nine or 10 testicular follicles spring from this germinal mass. Moreover, distributed over the body of the cercaria are 12 salivary glands, 8 mucous and 4 granular, all of which communicate with the mouth by means of a common col-

lecting canal. The body of the cercaria is covered with minute spines.

The protonephric apparatus of the larva of the *Schistosoma mansoni* is, on the whole, similar to the excretory system of the cercaria of the *Schistosoma japonicum*. It is characterized by 5 pairs of flame cells, 4 of which are situated along the body, and 1 at the root of the tail. The collecting tubules, anterior and posterior, are longer than the excretory capillary tubules.

The anterior collecting canal in the pre-acetabular region receives 2 capillaries from the flame cells, and the posterior one in its turn 2 capillaries: one from the flame cell of the posterior tip, and the other from the cell situated at the root of the tail.

The nervous system fills the space lying between the anterior portion of the acetabulum, the outer lip of the glandular ducts, and the posterior portion of the oral sucker.

The tail is strong, muscular, and bifurcated at the beginning of its 3d terminal. The size of the cercaria is as follows:

Body	130 micra by 55 micra
Tail	180 micra by 23 micra
Bifurcation	45 micra
Oral orifice	30 micra by 35 micra

In our investigation of the intermediate host of the *Schistosoma mansoni*, we had the opportunity of exposing to contamination a large number of animals susceptible to infection by *Schistosoma mansoni*. The animals were exposed for some time to the action of water containing adult cercariae. Under these conditions and when a goodly number of larvae are available, the infection is easily accomplished, and judging from experiments made consecutively, it requires a minimum of 5 minutes to produce the contagion. Depilation is not necessary in the case of white or domestic rats, inasmuch as the infection is always readily caught.

The route followed by the larva across the mammal is as follows: The cercaria attacks the skin with the capillary ends which are the meatus through which the ferments secreted in the cephalic glands escape. During this phase of the attack, the cercaria loses its tail and penetrates into the host. This penetration may be the work of a few minutes,

or it may require more time. As a general rule, 2 or more days are needed for it to enter the venous circulation, proceeding immediately to the heart, and thence to the lung from the capillaries of which it pursues its way to the arterial circulation. It is regularly distributed in the systemic circulation, its presence being easily detected during this period in the perifery and in the mesenteric system. The latter route carries it to the portal system, which is the only place suitable for its growth. Its progress from the skin to its favourite spot, the liver and its veins, is necessary for the worm to acquire, in addition to a certain amount of development, the necessary immunity against the organic humours. No sign of the digestive tubule is noticeable until the worm has reached its favourite spot in the body of the mammal host.

When the worm has succeeded in entering the portal system, it grows rapidly until it acquires size and strength enough to migrate to the mesenteric veins.

Eighteen days following the experimental infection, male worms are to be found in the liver, in which the digestive tubule is clearly visible, as also are the testicles. Notwithstanding repeated examinations, we were unable to find any female Schistosomes in the hepatic veins during the first month of the experimental infection.

In animals exposed to infection through the skin, examples of Schistosomes in copulation are noticeable in the portal veins during the 7th week, and only at the end of 2 months is it possible to discover the presence of eggs with lateral spine in the faeces of the infected animal.

In the account forwarded to the Colonial Office of Hygiene of Great Britain, Leiper (1908) states that in the cases of mixed infection, (*Schistosoma mansoni* and *Schistosoma haemætobium*) he had succeeded in separating the male Schistosomes into 2 groups: Some with 4 angular testicles, and the others with 7 or 8 small testicles. This writer has proved that the worms with 4 testicles were always joined to the females which produce eggs with terminal spine. Our investigations, like those of Leiper, have demonstrated that the males with from 7 to 10 testicles are always in copulation with the females which produce eggs with a lateral spine. We have been able to discover this disposition of the

number of testicles characteristic of the *Schistosoma mansoni* in the cercaria itself.

The Schistosomes obtained by infection in laboratory animals do not attain the size and vigour of those which have grown in the usual hosts by natural contagion, so that the differential features relative to their size and dimensions are of no importance. That is not the case, however, with some other particulars which we are going to indicate: The 2 lateral branches of the intestines meet before the acetabulum; the intestinal caecum is longer, and the spiracles of the males are much smaller than those of the *Schistosoma haemætobium*.

The females, obtained experimentally, present in their interior a single egg with lateral spine; the ovary is situated in the anterior portion of their body in the bifurcation caused by the 2 branches of the intestinal canal.

When intense experimental infections are effected, especially in domestic rats, the hepatic tissue presents under the microscope a characteristic colouration: on its surface are seen white patches alternating with dark spots. An examination of the scuts under the microscope discloses the disappearance of the hepatic tissue invaded by a conjunctive element of new formation. It is easy to detect the presence of worms in copulation in the interior of the hepatic veins. The presence of eggs with a lateral spine can also be detected in the remaining organs, as the interesting studies carried out by Rísquez (1916) in the Caracas Institute of Pathological Anatomy go to prove.

In our description of the way in which the infection of man and of animals was effected, on one occasion we indicated that notwithstanding the fact that the cercaria as a general rule penetrates into the organism through the skin, we had also obtained contamination *per os;* but as some have contended that the acidity of the stomach destroys the cercariae, and that these experiments are of no practical importance, we think, from experimental observations and from the fact already demonstrated, that parasites like *Anchylostoma duodenale* Miyagawa (1916) and the pathogenic germs like the *Spirillum cholerae* Sanarelli (1916) can penetrate the buccal, pharyngeal, and esophageal mucosa — we think that infection can be produced without the necessity of the larva

reaching the stomachal mucosa. These experimental facts are also supported by the observations of Day, mentioned by Leiper (1918) from which it is gathered that one of the causes which contribute to the propagation of Schistosomiasis in Egypt is the daily nasal and oral ablutions ritually practised by the Mussulman population.

We shall end this exposition with the following note relative to the distribution of Schistosomiasis in Caracas, and the sanitary measures adopted for its eradication.

Up to the year 1916, *Schistosomiasis mansoni* was observed in Caracas to an alarming extent, in places with a very thin subterraneous stratum contiguous to the alluvial soils of the River Guaire, where pools are constantly forming, and in which the *Planorbis guadelupensis* live and thrive. Sluggish irrigation canals serve, also, like the River Guaire, as a home for this mollusc. During our excursions in the environs of Caracas, for the purpose of ascertaining the distribution of the snail-host, we noticed that the majority of the inhabitants of these places for domestic purposes used water taken from canals and pools. In some canals around Caracas we found the *Planorbis guadelupensis* naturally infected in alarming proportions: from 1,000 specimens of mollusc, 150 turned out to be infected. The area contaminated by the *Planorbis guadelupensis* was limited to a small portion of the Valley of Caracas, which has greatly facilitated the adoption of prophylactic measures for diminishing, among other factors, the propagation of the malady.

The destruction of the cercariae in the water is a process which constitutes an incomplete prophylactic measure, and which, to produce positive results, requires the employment of a great quantity of chemical products which are generally inefficacious.

For some time back, or to be more precise, since 1922, the coprological examinations made by different experimenters have shown a marked decrease in the percentage of infections among the inhabitants of the environs of Caracas. For example, according to data furnished by Rísquez from the statistics of the Hospital Vargas, in 1916 the percentage of infected persons was 28%; at present, the presence of eggs with lateral spine has been discovered in only 5% of the patients. The data of the Public Health Department —

based on many examinations of faeces — also reveal a marked decrease in the number of infections.

From our own personal experience we may state that, from 600 analyses of faeces made in our laboratory, we have been able to discover infection in only 5 cases. This deminution of Schistosomiasis in Caracas is due to the following causes:

1. The publication of the way in which the malady was transmitted. Indeed, public lectures and the daily press especially, have awakened a healthy and beneficial foresight in the minds of the people, thus rendering the fight against the malady an easy affair.

2. The measures adopted by the Sanitary Authorities, which forbade the cultivation of lands bordering the river Guaire, which were veritable breeding places of the intermediate host, and which maintained a high percentage of infection among the farming population, in some cases 30%. The draining of those lands, effected since 1921, and the prohibition of all further cultivation of irrigated soil, have brought about the total disappearance of the intermediate host.

In other places, and especially on some sugar-cane plantations around the city, the people have had the foresight to clean the canals periodically and to leave them dry for a period of 10 to 15 days. These measures have resulted in a large diminution of the number of *Planorbis guadelupensis*.

3. The systematic application of the method of Christopherson (1918–19) to all infected persons. Indeed, the treatment of our *Schistosomiasis mansoni* with cream of tartar emetic not only has, as a general rule, effected its cure, but it is, in our opinion, the only process capable of producing an efficacious prophylaxis. The greater part of our practitioners are familiar with its technique, and the number of cures effected in hospitals and private clinics can be numbered by the hundred.

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DISCUSSION

Dr. Friedrich Fülleborn (Opening the Discussion). — I wish to congratulate Dr. Iturbe for the splendid work done by him and by Dr. Gonzales on *Schistosomum mansoni*; it is of great value, not only in general, but especially also for his country, Venezuela, because as Dr. Jesus Risquos has shown, in about one-fourth of the post-mortems done in Caracas, the eggs of the parasites are found in the tissues. Indeed, only a small percentage of the carriers of the *Schistosomum mansoni* will have remarkable clinical symptoms, but on the other hand sometimes the infection produces severe consqeuences.

The splendid film shown this evening by Dr. Iturbe will contribute a good deal toward public instruction, and therefore toward the prophylaxis of the disease. Especially in Caracas it is true that the danger from bathing in contaminated water is practically no longer present, since the splendid new system of drainage of the capital has become effective.

Dr. Henry Rose Carter. — I really have nothing to say about the modern history of *Schistosoma mansoni,* but a little of the early history may be of interest. My attention was first drawn to it in a book by Sigaud, on the "Climate and Diseases of Brazil," published about 1843. He mentions a disease — common in Brazil, especially in the district from about Bahia to Pernambuco — known as "O bicho." His description was that of an acute proctitis, not infrequently resulting ultimately in gangrene and death. The specific treatment was heroic: an enema of an extract of "African pepper" (Cardamons) in rum and lemon juice. If this

gave so much pain that it could not be retained, recovery was possible. If it could be retained, *i.e.*, if the part was insensitive from gangrene, he died. Sigaud thought that this disease, with others, had been imported from Angola, West Africa.

Père Labat, who gave us the account of the importation of the *Mal de Siam* into Martinique (from Pernambuco) in 1690, later went as a missionary to the island of São Thomé, Portuguese West Africa. There he not only recognized the *Mal de Siam* (which he says should be called "Mal de St. Thomas" as it was prevalent there) but also this "*O bicho*," called by him "*Mal de Cu*," Cu being Portuguese for breech. He also mentions as a specific treatment the use of lemon juice as enemata and of lemons cut in quarters as suppositories.

As for the *name "O bicho*," it is one of the misfortunes of that time that autopsies, which should clear up diagnoses, in the Brazils and Portuguese West Africa, confused them. The graduates from the really progressive University of Coimbra made autopsies — "anatomies," as they were called — on the strange and unknown diseases with which they met in foreign parts. In practically all of them made on men living long in Brazil or West Africa, lumbricoid worms were found in numbers in the intestines. These were considered the cause of the disease and of death, and we accordingly find the most diverse diseases named; as this disease in 1604 at Angola: scurvy a few years earlier, and yellow fever at Pernambuco in 1684, all grouped in one as "O bicho" or feminized as "A bicha" — "the living creature."

To add to the confusion, the Dutch writers, knowing that lemon juice was held a specific for "O bicho," and not knowing how it was used, registered the *bicho* of West Africa as scurvy. These autopsies make much trouble for us.

Colonel Bailey K. Ashford. — I should like to ask the author of the paper what he considers the incidence of morbidity among those infected in Caracas. In Porto Rico we found schistosomiasis in 1904, and published an account of it in a detailed history in our report "Uncinariasis in Porto Rico." It was a case of true "Schistosoma dysentery." We made a very determined effort to learn something about the etiology and life-history of the organism, as we began finding it among our country patients quite frequently. We found the disease especially in children who bathed in a small stream tributary to the river "Vivi" in Utuado. We ascertained that it did not come from drinking the water, but soon convinced ourselves that it came from bathing in the water. Unfortunately we had no time to divert from our main work and study it further. We should like to know what proportion of people *infected* are suffering from the *disease* in Venezuela. It requires a certain

number of parasites to cause symptoms. In Porto Rico a number of people are infected, but very few suffer from the disease.

Reply by Dr. Juan Iturbe. — From 1% to 2% of those infected suffer from the disease.

SOME OBSERVATIONS ON *GRANULOMA INGUINALE* AND CULTURAL STUDIES OF THE DONOVAN BODIES

FOSTER M. JOHNS, M.D.

INTRODUCTION

Following the brilliant work of Aragao and Vianna,[1] of the Oswaldo Cruz Memorial Institute, in 1913, confirming the etiologic relationship of the bodies described by Donovan, and adding the discovery of the specific curative effect of tartar emetic given intravenously, the infectious granulomatous process first described by Colonel McLeod in 1882, from India, is now universally recognized as a specific disease. While *granuloma inguinale* has been recognized as occurring principally in tropical countries, it has been reported from many cold climates and is probably endemic the world over.

The literature was exhaustively studied by Gage,[2] of New Orleans, in 1923, who found that up to that time only 55 cases had been recorded from the entire United States and its dependencies. The earlier work of Reed and Wolff,[3] followed by the work of Gage, has stimulated us in the search for cases of this disease. As a result, during the past 12 months, 94 cases have been admitted to the wards of the Charity Hospital of New Orleans alone, to say nothing of the clinic cases of not sufficient severity to be admitted to the wards. A rough estimate of the total number of cases under treatment in the various hospitals and clinics in New Orleans would run into the hundreds.

While it is true that our climate is semi-tropical in character, it is very probable that, with a more widespread knowledge of the particular methods of microscopic examination necessary, this fourth venereal disease will be found to be of considerable importance.

With an unlimited supply of clinical material available, and with facilities for the study of these cases while under-

[1] ARAGAO and VIANNA: *Mem. do Inst. Oswaldo Cruz*, Rio de Jan., 1912, IV, 211.

[2] GAGE, I. M.: *Arch. Dermat. and Syph.*, 7:305, Mar., 1923.

[3] REED and WOLFF: *New Orleans Med. and Surg. Journ.*, 74:25, July, 1921.

going treatment, I have been particularly interested in studying certain phases of the subject, the results of these studies forming the basis of this communication.

DISTRIBUTION OF LESIONS

While *granuloma inguinale* is most often found in the inguinal regions, on the *glans penis* or the *vulvæ*, there seems to be no limit to the area that may be involved. We have seen several cases in which extra-venereal granulomatous processes remained long undiagnosed, until a chance scraping was made and stained by Wright's or Giemsa's stain and the diagnosis established. (Fig. 2 gives a general view of the usual penile and inguinal involvement.) We had one case which presented lesions involving the chest, cheek and lip (Fig. 1). The lesion in this case also extended over the lip and gums and onto the roof of the mouth. One case had a lesion on the sole of the foot, from which site Donovan bodies were recovered (Fig. 3). This case also had extensive penile lesions. Several of our cases gave no evidence, by scars or history, of venereal lesions and yet presented marked corporeal lesions that had been variously diagnosed as *blastomycosis*, *tuberculosis cutis*, or syphilis.

Many early penile lesions are still incorrectly diagnosed as chanceroid. A search for Donovan bodies in all penile lesions of several weeks' duration that presented a negative dark-field examination for treponema, and no inguinal glandular enlargement has resulted in uncovering many early cases of granuloma.

We have not observed a single case in a Caucasian that has been confirmed by microscopic examination. A few of these have been recorded. I can recall two clinic cases that presented the massive inguinal, abdominal and scrotal lesions, with complete erosion of the *glans penis*. They were not diagnosed at the time, but the characteristic pictures presented make me feel now that they were certainly this same disease.

DONOVAN BODIES

An exhaustive study in fresh preparations, various suspension fluids, smears and sections has failed to add any-

Fig. 1

Fig. 2

Plate I

thing new to the morphology of the bodies as first described by Donovan in 1905 (Fig. 14). It is my conclusion that the organism is a protozoan parasite, and not a simple encapsulated bacillus,— for the following reasons:

I. In fresh preparations the organism appears as a plump, rounded, glistening mass of protoplasm, the full size of the well-stained organism. It is only by full differentiation of the well-stained parasites that the chromatin element becomes visible.

II. Donovan bodies are not stained by any of the simple stains or more elaborate, purely capsular stains that demonstrate any of the cultivatible encapsulated organisms. The tendency has been to incorporate this organism into the Friedlander group. The respiratory forms of this group are easily demonstrated in pus smears with any of the simple stains.

III. In various culture media or suspension fluids, the bodies may be noted to disintegrate slowly into a granular, pinkish staining mass that does not in any way parallel the disintegration of bacteria. This was noted first in certain cells from direct smears of lesions by Aragao.[1]

IV. Definite proof of the cultivation, as bacteria, of the bodies in question is lacking.

All of the bacteria that we have been able to cultivate from lesions which were in any way suggestive of the morphology of Donovan bodies, could be demonstrated in the stained smears of the inoculum. (Fig. 15 shows Gram (–) diplobacilli in a pus cell, in comparison with the Donovan bodies in the mononuclear. These diplobacilli were easily overstained with Wright's stain, to produce a capsular appearance. This capsule could not be demonstrated with a Giemsa stain.)

On the other hand, I have not been able to demonstrate the rather fanciful forms suggestive of herpetomonads or crithidia, as drawn by Sir R. M. Carter,[2] and I have not been able to confirm the opinion of some authors that the zoögleic masses (Fig. 13) represent a modified form of schizogony. Thin spreads of material stained to bring out and

[1] ARAGAO, H. DEB.: *New Orleans Med. and Surg. Journ.*, 70:369, 1917.

[2] CARTER, R. M.: *The Lancet*, Oct. 15, 1910, 1,128.

Fig. 3

Fig. 4

Plate II

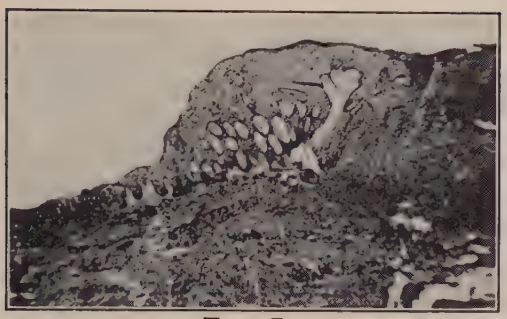


Fig. 5

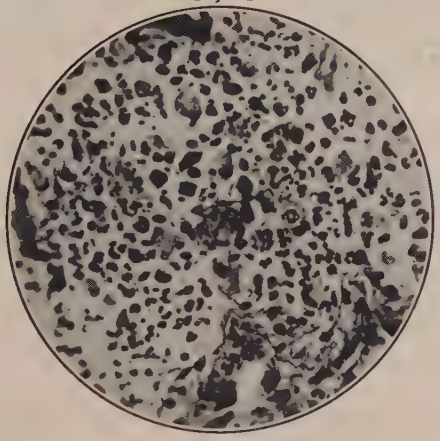


Fig. 6

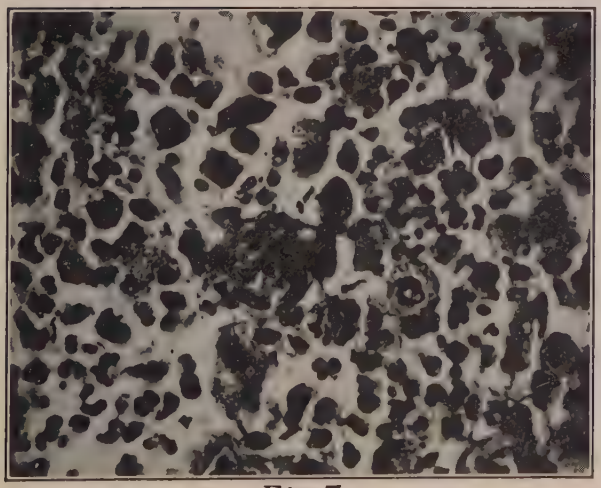


Fig. 7
Plate III

differentiate the blue cytoplasm have shown only masses of single or diplococcoid forms, indicating a simple binary fission as the only method of reproduction (See Figs. 11 and 12).

V. The intracellular parasitism exhibited, while not exclusively a protozoan trait, is certainly more often encountered in protozoal infections. It is very evident that the only extra-cellular phase of this parasite's life is incidental to the death of the cell host and its phagocytosis by another endothelial cell.

VI. The striking specificity of tartar emetic in this disease runs parallel with its action in other known protozoal infections.

The Production of the Lesion

The number of organisms that may be tolerated by a cell without damaging its chemical composition, as shown by delicate staining reactions, makes one wonder in just what manner the gross pathologic lesion is consummated. (Fig. 5, advancing edge of granuloma; Fig. 6, high, dry magnification in granulomatous tissue; Fig. 7, high magnification of same field showing blood vessels, endothelial cells containing Donovan's bodies, and the general cellular reaction.) It would appear that the phagocytosis by proliferated endothelial leucocytes is a normal function of these cells, but the phagocytosis and intracellular multiplication of a living organism in these same cells when *constituting the walls of a blood-vessel* stimulate a more rapid proliferation, resulting in a greater aggregate of blood vessels, of which granulation tissue is chiefly composed. This undue proliferation of endothelial cells also results in many vessels becoming occluded by masses of these cells, many of which contain Donovan bodies (Figs. 8, 9 and 10).

Relapses Following Treatment

Practically all of the later papers relate the high incidence of relapse following complete epitheliazation of the lesions during continuous treatment with tartar emetic. These relapses occur almost invariably where the advancing edge of the previous lesion terminated (see Fig. 4). Either the

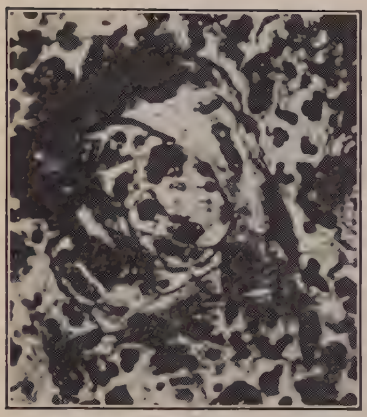


Fig. 8

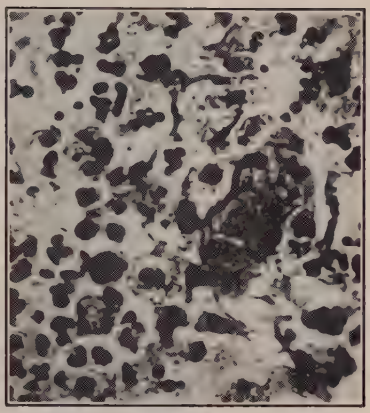


Fig. 9

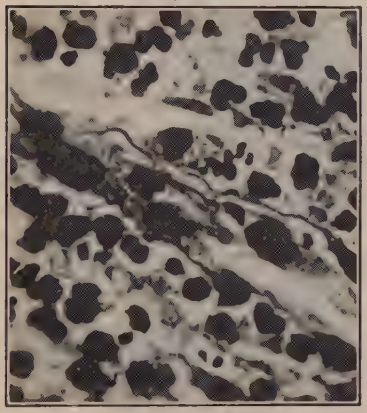


Fig. 10

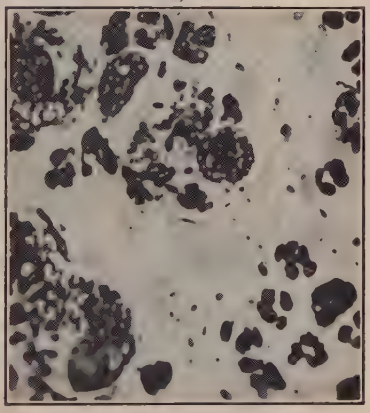


Fig. 11

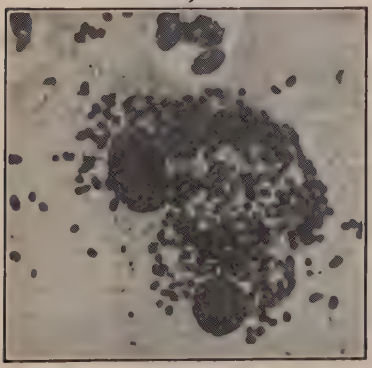


Fig. 12

Fig. 13

Fig. 14

Plate IV

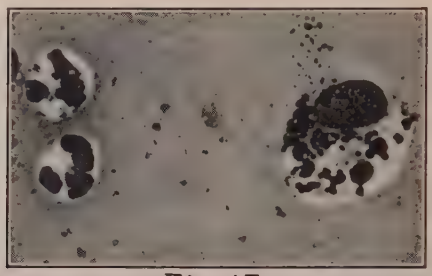


Fig. 15

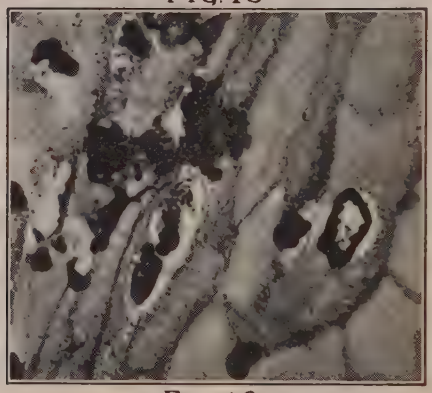


Fig. 16

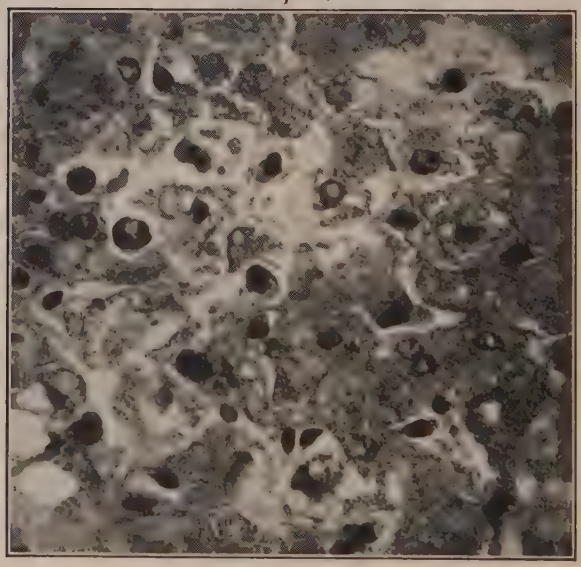


Fig. 17

Plate V

whole margin of the former lesion again undergoes granulomatous proliferation, or several foci begin at different points along the margin of the cicatrix.

A close study of Giemsa-stained tissue-sections taken from the advancing edge of the lesion has revealed an occasional endothelial cell filled with Donovan bodies embedded between the epithelial cells of the grossly-hypertrophied epithelial papillæ (Fig. 6). It is highly improbable that tartar emetic from the blood stream can penetrate between the epidermal cells in sufficient concentration to destroy these protected parasites. When it is remembered that the lesions heal by cicatrization, and are covered by epitheliazation from the remains of these papillæ, it seems to be reasonable to believe that the parasites in these cells are responsible for the re-inoculation of the lesion. The organisms are liberated by the natural erosion of the hypertrophied papillæ, which is the last step in the healing process, and which probably occurs after the gross lesion appears to be practically well.

TREATMENT WITH TARTAR EMETIC

The usual plan of treatment is from 5-12 cubic centimeters of a 1% solution of tartar emetic given intravenously, at 2 or 3 day intervals, until the lesions are healed. Most of the authors recommend several subsequent courses of medication, to forestall relapses.

Smears studied from numerous cases under treatment show that following the 5th or 6th dose it is practically impossible to find Donovan bodies. The laying down of fibrous tissue and the epitheliazation of the comparatively large surfaces denuded in the inguinal, perineal and corporeal lesions, proceeds at a much slower rate than the disappearance of the organisms. Complete healing often requires from 1 to 3 months, according to the area of the lesions, the general health and care of the patient, etc.

The entire literature to date does not record a single case of granuloma with a fatality attributed to tartar emetic. There have occurred 3 deaths in cases undergoing treatment in New Orleans, 2 of which presented all of the indications given in the textbooks for tartar-emetic poisoning, viz, multiple punctate hemorrhages, no post-mortem clotting

of the blood, and acute yellow atrophy of the liver. (Fig. 17 shows a section from the liver of one of these cases, with granular degeneration of parenchymal liver cells and obliteration of the nuclei. Note, in contrast, the staining of the nuclei of the other cells.) Both of our fatal cases resulted from doses of 18 cc. and 20 cc., respectively, of a 1% solution that had been stepped up from 4 cc. by an increase of 2 cc. per injection. I would infer from this that the average case usually receives at least ½ of the lethal dose over a long period of time, and that there must result considerable liver damage.

In view of the fact that tartar emetic is said to be a cumulative drug, that proportionately few doses cause almost complete disappearance of the etiologic agent, and in view of the probable damage to the liver by long-continued sublethal doses necessitated by the length of time required for healing to take place, I would suggest that interrupted courses of treatment be given instead of the usual almost continuous plan of medication.

CULTIVATION EXPERIMENTS WITH DONOVAN BODIES IN VIVO AND VITRO

Aragao and Vianna,[1] Walker,[2] and Randall, Small and Belk[3] have all cultivated a gram-negative encapsulated bacillus of the Friedlander type from a few *granuloma inguinale* lesions, and they have drawn rather strong inferences that this organism was probably identical with Donovan bodies.

If granuloma is a bacterial disease, then we would possess the first synthetic specific drug against the vegetable parasites in the history of medicine. It seems, therefore, most important that these findings be corroborated if possible.

The Friedlander-type bacillus cultivated by the above-named authors was markedly pathogenic for the usual laboratory-test animals. In contrast with this, currettings from "surface-cleansed" lesions containing numerous demonstrable Donovan bodies were absolutely non-pathogenic for dogs, rabbits, guinea pigs or mice. In collaboration with

[1] ARAGAO and VIANNA: *Mem. do Inst. Oswaldo Cruz*, Rio de Jan., 1912, IV, 211.
[2] WALKER, E. L.: *Journ. Med. Res.*, 37:427, Jan., 1918.
[3] RANDALL, SMALL and BELK: *Surg., Gynecol. and Obstet.*, 34:717, June, 1922.

Dr. I. M. Gage, we have repeatedly injected or transplanted scrapings, tissue fragments and tissue implants into all of these animals intradermally, subcutaneously, intraperitoneally, intratesticularly, in vesicles produced by cautery and old traumatic lesions with granulomatous exuberations, without producing any apparent reproduction of the organism or consistently causing death of the test animals.

In addition to the usual culture media, we have tried many grades of hydrogen-ion concentration, with and without the sugars, in air, nitrogen and hydrogen atmospheres. Fragments of tissue containing numerous organisms were followed to disintegration in citrated rabbit's blood, partially and completely hemolyzed blood containing varying amounts of agar, hydrocele fluid, and water or semi-solid agar with and without tissue (rabbit kidney), many cultures remaining sterile for months. We are therefore unable to substantiate any claim that Donovan bodies have been cultivated.

EXPLANATION OF PLATES

PLATE I. Fig. 1. Lesions of *granuloma inguinale* on neck and face.
Fig. 2. Typical inguinal lesion.

PLATE II. Fig. 3. Lesion of granuloma on palm of foot.
Fig. 4. Extensive relapse along former advancing edge of lesion.

PLATE III. Fig. 5. Section through advancing edge of lesion. Low, dry magnification.
Fig. 6. Area of granulomatous proliferation. High, dry magnification.
Fig. 7. Same field under higher magnification. Note endothelial cells filled with Donovan bodies, and general type of cellular reaction.

PLATE IV. Figs. 8, 9 and 10. Donovan bodies in endothelial cells still attached to the blood-vessel walls.
Figs. 11 and 12. Donovan bodies in smear preparations.
Fig. 13. Zoöglea masses.
Fig. 14. Donovan bodies well differentiated to show the division of the chromatin.

PLATE V. Fig. 15. Donovan bodies (and zoöglear masses) in an endothelial cell, in comparison with a Gram-negative diplobacillus phagocytized by the pus cell.
Fig. 16. Donovan bodies in an endothelial cell embedded in the epithelial cells of a grossly hypertrophied papilla.
Fig. 17. Section of liver from fatal case of tartar-emetic poisoning. Note complete granular degeneration of liver parenchyma.

DISCUSSION

Dr. J. G. Thomson (Opening the Discussion).— Pathologists in the Tropics and elsewhere are often called upon to examine scrapings or smears from ulcers in various parts of the body — for example, from the face, arms, legs or genitalia.

One of the commonest organisms found associated with these chronic ulcerated conditions is a spirochæte. There is, however, no proof that these various types of spirochætes are causal factors in the production of the lesions with which they are associated, and although they have been found in *Granuloma inguinale* it is not generally accepted that they are the causal organism of that condition.

The discussions in the *section* of dysentery have shown us that the pathogenic role of the intestinal flagellates is extremely doubtful; in fact, there is a considerable amount of evidence that all the intestinal flagellates so far described in man are simply harmless commensals associated with dysentery, diarrhœa and other conditions.

The point I wish to emphasize is that the finding of an organism either bacterial or protozoal in nature, associated with a pathological condition, does not mean we have discovered the true cause of the disease.

Dr. Johns in his excellent paper has described in *Granuloma inguinale* the so-called Donovan bodies. These seem to be tissue parasites, but as I have not seen these films I am quite unable to offer an opinion as to whether they are bacterial or protozoal in origin.

Further observations on this interesting disease are necessary and I am sorry that, owing to the fact that I have not personally investigated this condition, I am unable to discuss the valuable work done by Dr. Johns.

Dr. Hideyo Noguchi.— My interest in inguinal granuloma was aroused through the fact that in these ulcers there have been one or more varieties of spirochætes described in the literature. During our recent expedition to Bahia, Brazil, I was given an opportunity to study a couple of typical cases of this disease.

One was a female adult patient of Dr. Flaviano Silva, in the Santa Eliza Hospital, in Bahia, who exhibited an extensive surface of granular, readily-bleeding, tender ulcer, covering the entire vulva and both sides of the inguinal region. Smears were made from a fragment of the lesion removed by Dr. Silva and after fixing in buffered formalin (Tilden) and methyl-alcohol, they were stained with Giemsa or saturated alcoholic solution of basic fuchsin. It may be mentioned that the buffered formalin fixation enables one to stain even *Treponema pallidum* with the fuchsin solution in a few seconds and it was hoped to stain the Donovan bodies more distinctly by this method than by the Giemsa solution.

The smears showed an enormous number of minute spirochætes which morphologically resembled *Treponema genitalis*, the smallest saprophytic spirochæta found in the smegma flora of normal

genitalia. There were also numerous microphages containing diplococcoid organisms, as well as a few large mononuclear cells occasionally showing intracellular diplococcoid or diplo-bacillary organisms not unlike the *Calymmatobacterium granulomatis* of Aragão and Vianna. (The latter form was demonstrated to me by Dr. Aragão himself, at Rio, in his original preparation, before we arrived at Bahia.) The fresh scrapings and fragments of the lesions were also utilized for dark-field examination and cultivation on different media. The emulsion contained the above-mentioned spirochætes in fairly motile state, but I was not sufficiently experienced to distinguish the Donovan bodies from the diplococcoid forms present simultaneously. Attempts to isolate the Calymmatobacterium on serum-agar plates have failed, but a gram-negative diplococcus resembling *Micrococcus catarrhalis* was obtained.

On the other hand, the minute spirochæta contained in the emulsion was obtained in a mixed culture (using fresh tissue and serum-agar) which was finally purified after my return to New York. So far, pure cultures of this spirochæta have failed to produce any lesion in the skin of baboons or *Macacus rhesus* monkeys. Perhaps this organism is of smegma origin.

I am much impressed with the thoroughness with which Dr. Johns tried to isolate the Donovan bodies, and with the negative results he nevertheless has so far obtained with this organism. Of course, the difficulty of staining or cultivation may be explained by the possible strain-variations of the Donovan bodies existing in those found in North America and those in Brazil. Let me express my hope that Dr. Johns will eventually succeed in confirming the work of Aragão — one of the most careful and competent protozoölogists we now have — and of the late Gaspar Vianna, who was the first to introduce the tartar-emetic treatment for *Leishmaniasis*. Dr. Johns has done much by showing us the difficulties of obtaining a culture of Donovan's bodies, be they protozoa or bacteria, thus inviting others to take up this problem.

Dr. Charles C. Bass.— I wish to call attention to the fact that this work of Dr. Johns and the other workers in New Orleans demonstrates the wide prevalence of a disease, commonly thought to be a tropical disease, which has formerly not been recognized. It is not that this disease has just appeared in New Orleans. Those of us who have been there for some time can recall cases treated 10 to 15 years ago. The disease probably occurred then as frequently as it does now. It was simply overlooked.

Another point I wish to emphasize is that made by Dr. Johns, that the use of treatment such as tartar-emetic for a prolonged

time, while waiting for the healing over of the lesion, is unscientific. I am not quite sure but that the point of second importance in this paper is, calling attention to the fact that it is likely to be harmful to continue treatment for a long time after the organisms have practically disappeared. This very practical suggestion, if properly taken into consideration, will probably save a good many from poisoning and from loss of life from tartar-emetic.

Dr. R. W. Runyan.— Dr. Johns has called our attention to the possible dangers of long continued administration of tartar-emetic. The healing of some of these lesions is so slow that if the administration of the drug were continued until the wound heals, there would undoubtedly be many bad results.

Granuloma Inguinale as far as I have seen it is frequently complicated by true venereal disease. In one recent case there was the most remarkable improvement following first few injections of tartar-emetic, but in a week or ten days the condition was at a stand-still. Having discontinued the tartar-emetic at the end of 10 days, and the inguinal ulceration remaining practically stationary for two or three weeks and not reacting to a second series of tartar-emetic injections, had a Wasserman reaction made and this being positive I gave a few injections of neosalvarsan and the ulceration promptly healed. In a second case in which Donovan bodies had also been found, I had little or no results following 10 injections of tartar-emetic. Wasserman was negative in this case, but I believe I must have been dealing with a complicating chancroidal infection, because it promptly healed following thorough cauterization and local applications of mercurochrome and iodoform.

The possibility of complications of this type should be kept in mind and I feel sure that in at least some of the more resistant cases syphilitic and chancroidal infections are the cause of delayed healing.

Dr. Foster M. Johns (*Closing the Discussion of His Own Paper*). — Dr. Runyan brought out a point regarding something that we see all the time — that is, errors in diagnosis. Bacteria, heavily stained, may look like Donovan bodies. I have not found Donovan bodies except in endothelial cells,— and considerable care must be exercised to limit the diagnosis to the finding of Donovan bodies in these cells only. Of course, you find many cells that are broken.

I am quite sure that in many cases the liver is hopelessly damaged when the treatment is carried on for any length of time. I believe that after the organisms have been reduced to the minimum, you can allow a 2 or 3 weeks' rest, during which time healing will continue just as rapidly, as the number of specific organisms present is certainly no factor during this time.

ACTION OF CERTAIN BIOLOGICAL, CHEMICAL, AND PHYSICAL AGENTS UPON CULTURES OF LEISHMANIA; SOME OBSERVATIONS ON PLANT AND INSECT HERPETOMONADS

Hideyo Noguchi, M.D.

Cultural Requirements of Leishmania

Rogers was the first to show that the non-flagellated forms of Leishmania develop into flagellates in appropriate fluid media, and in this form can be maintained in an indefinite series of subcultures. The blood agar slant of Novy and MacNeal, or the same medium without the addition of peptone and meat-infusion (Nicolle) has been widely adopted for the cultivation of Leishmania, the organisms growing in the condensation water and occasionally even on the surface, as minute dew-point colonies.

Wenyon,[1] in 1921, reported good results in the cultivation of protozoa by means of a semi-fluid agar medium to which about 1 cc. of rabbit whole blood is added to each tube at the time of use; and Kligler[2] employed a similar medium, but with the addition of 0.1% of glucose, for *L. tropica*. I have found that a medium in use by me for several years for the cultivation of the leptospira group yields an excellent growth of Leishmania, 2 strains of *Leishmania brasiliensis* having been isolated by this means from 6 cases selected by Dr. Lindenberg among the patients in his Leishmaniasis ward of the Santa Casa Hospital of São Paulo.[3] One of the advantages of this medium is that the organisms, once grown, remain viable for many months without subculturing, and that the medium remains serviceable for many weeks when preserved at a low temperature (18° C. or below). Another,

[1] Wenyon, C. M.; *Trans. Roy. Soc. Trop. Med.*, 1921, xv, 141-155.

[2] Kligler, I. J.; *Amer. Journ. Trop. Med.*, 1924, iv, 69.

[3] Noguchi, H., and Lindenberg, A.; *Am. Journ. Trop. Med.*, in press.

perhaps more important, advantage is the readiness with which a large quantity of the organisms can be obtained. The growth of the various species of Leishmania on this medium becomes readily recognizable after a few days (at 18–20° C.) as a grayish-white surface haze, which continues to increase in depth until within a week a scum-like colony of 2–4 mm. in thickness covers the uppermost portion of the medium. When the rich growth is skimmed off, another mass of organisms grows in the same tube, and the process can be repeated every week or so until the medium is exhausted. The pure mass of organisms thus obtained is composed of flagellated and actively motile forms. If the first growth is not removed, the organisms remain viable for several months but ultimately undergo the usual degenerative changes.

Leishmania infantum,[1] *Leishmania tropica*,[1] and *Leishmania brasiliensis* have grown chiefly on the surface. The strain of *Leishmania donovani* in my hands[1] has shown a tendency to grow also in a zone several centimeters below the surface, where oxygen does not freely penetrate. No growth has been obtained in an atmosphere of nitrogen, hydrogen, or carbon dioxide, — hence all the Leishmania culture strains are to be regarded as obligate aerobes. The addition of NaOH to the medium beyond pH 8.2, or of HCl beyond pH 5, renders it unsuitable for the growth of these organisms.

BIOLOGICAL PROPERTIES OF LEISHMANIA

Immunity

The relation between *Leishmania tropica* and *Leishmania donovani* has been widely discussed, but no differentiation has been brought out from the laboratory standpoint. Animal experiments have seemed to indicate the identity of *Leishmania donovani* and *Leishmania infantum* (Nicolle and Laveran).[2]

[1] The strains of *Leishmania donovani* and *L. infantum* were obtained through the courtesy of Prof. C. A. Kofoid, of the University of California; the strain of *L. tropica* was furnished me by Major Henry J. Nichols, of the Army Medical School.

[2] LAVERAN, A.; "Leishmanioses," Paris, 1917, page 55.

Much of the unsatisfactory test-tube experimentation of the earlier days was undoubtedly due, at least in part, to the lack of means of obtaining sufficient quantities of the organisms for immunity work. With cultures grown on the semi-fluid medium described, however, it has been possible to immunize rabbits with the various strains of Leishmania. Rich live cultures of a given strain were injected intravenously on 4 successive occasions at 5- to 7-day intervals. The serums of these rabbits were tested for agglutination with the homologous and heterologous strains, and the results were clear-cut and decisive. The anti-*donovani* and anti-*infantum* serums agglutinated *L. donovani* and *L. infantum* reciprocally, — that is, these 2 strains were serologically identical. On the other hand, neither of these serums showed any agglutinating property for *Leishmania tropica* or *Leishmania brasiliensis*. The anti-*tropica* serum agglutinated only the *tropica* strain and the anti-*brasiliensis* only the *brasiliensis*. The titres of these anti-serums were such that a 1:10 dilution caused a prompt and powerful agglutination, while 1:100 was moderately active against the homologous strains. The agglutination tests appear to permit the separation of at least 3 distinct species of Leishmania, (1) *L. donovani* of kala azar, and *L. infantum*, with their dominant visceral affinity, (2) *L. tropica* of oriental sore, with its essentially dermal effects, and (3) *L. brasiliensis* of the New World, with its pronounced mucodermal predilections. Cultures obtained on a medium containing 10% of homologous immune serum grow in small clumps, while the growth on media containing normal or heterologous (Plate A) immune serums is smooth and scum-like. The immunological differentiation of these 3 distinct species of Leishmania may have an important bearing on the future development of serum treatment or vaccination in various forms of Leishmaniasis. Because of the limited number (2) of Brazilian strains used in the present series of experiments, the possibility of the existence of other varieties among Brazilian cases is not excluded.

Resistance to Various Agents

As a means of obtaining information regarding the Leish-

mania as a living cell, various physical, chemical and biological agents have been applied to the actively growing flagellate forms of the 4 strains, *L. tropica*, *L. brasiliensis*, *L. donovani*, and *L. infantum*.

Tonicity. — Leishmania underwent instantaneous plasmoptysis when suspended in distilled water, the flagella becoming detached and immobile, and the cell-body breaking up into fragmented masses. The presence of 0.1 per cent NaCl prevented plasmoptysis, but the bodies became round, and the flagella rigid and swollen. In a 0.2 per cent NaCl solution the organisms were slightly swollen, but motile. A concentration of 0.3 to 0.9 per cent NaCl preserved Leishmania in excellent condition. Half-saturated NaCl made them appear rigid, shrunken, and refractile.

Acid and alkali. — HCl, added to a 0.9 per cent NaCl in a concentration of N/1 to N/10 promptly inhibited the motility of Leishmanias, the cells becoming highly refractile, but retaining the flagellum.

NaOH, added to 0.9 per cent NaCl in a concentration of from N/1 to N/10 caused cessation of motility, the cell bodies became indistinct, and in most instances the flagella dissolved within a few minutes. In 0.9 per cent NaCl with a pH of 8.2, the Leishmanias were all active.

All the strains grew well in medium with a pH of 5.08 to 7.21, but *L. tropica* grew well up to pH 8.8 and *L. infantum* up to pH 8.19. Rich growth of *L. brasiliensis* occurred at pH 7.7 and some growth at pH 8.19 but none beyond. *L. donovani* did not grow beyond pH 7.21.

Chemical and biological agents. — Saponin in dilutions of 1:10 to 1:10,000 killed the Leishmanias without dissolving them. Sodium taurocholate dissolved them in 1:100, but in 1:1,000 dilution a few organisms still survived. Sodium oleate destroyed them in 1:100 but not completely in 1:1,000. Ricin, dissolved in saturated NaCl 1:10, then diluted to 1:100 with distilled water to render the mixture isotonic, showed a definite immobilizing and clumping effect upon Leishmanias, while abrin of similar concentration had no perceptible effect. In higher dilutions ricin was ineffective.

Snake venoms, themselves of animal origin, were also tested for their effects upon Leishmania. The venoms of

Crotalus adamanteus (Florida rattlesnake), *Ancistrodon piscivorus* (water moccasin of the United States), *Lachesis flavoviridis* (*habu* of Formosa), *Lachesis lanceolatus* (South America), *Vipera russelli* (daboia of India), and *Vipera berus* (*mamushi* of Japan) exerted no effect upon the Leishmanias when used in a 1:200 dilution. On the other hand, the venom of the cobra (*Naja tripudians* of India) caused immobilization in 1:200 and 1:2,000, while the addition of lecithin rendered the cobra venom active against Leishmania in a 1:20,000 dilution; in venom of this concentration the organisms remained active until the lecithin was added. The activation by lecithin was also noticeable with the venoms of *L. lanceolatus*, *L. flavoviridis*, *Ancistrodon piscivorus*, and daboia, but scarcely at all with the venoms of the rattlesnake and the little Japanese viper. The leishmaniolysis by certain snake venoms in the presence of lecithin is analogous to the hemolysis occasioned by the same combination, and the comparative innocuousness of various snake-venoms upon a protozoan organism is a point of interest.

Effect of Chemotherapeutic Preparations

The effectiveness of tartar emetic in the treatment of leishmaniasis appears to be well established.[1] The exact manner by which these antimony compounds act upon the parasites in the human body is not known; hence it was of theoretical interest to inquire into the mechanism of the action of these drugs by way of test-tube experiments, of which 3 types were made: (1) the direct effect of drugs *in vitro* upon Leishmania; (2) the effect of the same drugs after being mixed with fresh animal-tissues (rabbit liver or kidney) *in vitro*; and (3) the effect of the drugs after having been introduced into the animal body, as determined by examining *in vitro* the effect of the serums derived from the drugged animals.

Of the antimony compounds, tartar emetic was dissolved in 0.9 per cent NaCl in concentration of 1:100. From these stock solutions further dilutions, corresponding to 1:1,000, 1:10,000, and 1:100,000 were prepared, and active Leish-

[1] WENYON, C.M.; *Trop. Dis. Bull.*, 1922, xix, 5, 185.

mania cultures were added to each. Tartar emetic in 1:100 solution killed the organisms promptly, but in a 1:1,000 dilution some were still alive after 1 hour, and a 1:10,000 dilution had no effect. Emetine hydrochloride killed the organisms in 45 minutes in 1:1,000 dilution, but not in 1:10,000 dilution. The addition of fresh rabbit kidney or liver emulsion to these drugs neither increased nor decreased their inherent toxicity for Leishmania: — that is, there was no immediate transformation of the drugs into a more toxic form by the action of fresh somatic cells *in vitro*.

Eight bismuth compounds, the tartrate, albuminate, citrate, oxalate, lactate, benzoate, subgallate, and acetate, were similarly studied, but their insolubility in water rendered the determination of their inherent germicidal action *in vitro* highly uncertain. They were inactive when used as suspended particles. Attempts to transform these substances into toxic form by grinding them with a fragment of fresh rabbit-liver were not uniformly successful, the tartrate being the only one which acquired a slight toxic effect after this treatment. The emulsion containing the tartrate in ratio of 1:100 had a definite injurious action upon the Leishmanias, but a ten-fold dilution of it exhibited only a slight inhibition of motility.

Ten arsenic compounds, including salvarsan, neosalvarsan, tryparsamide[1], and A 96,[1] were similarly tested. In direct action *in vitro* salvarsan and neosalvarsan killed the organisms in a 1:1,000 dilution and immobilized many in 1:10,000 within 2 hours, while tryparsamide and A 96 affected them only slightly in a 1:200 dilution. Salvarsan was used in a slightly alkaline solution (pH 7.4); the others were neutral and required no adjustment of reaction. Several arsenic compounds which were available for this series of experiments were omitted because they had to be dissolved by adding NaOH, and it had already been found that Leishmania was sensitive to any slight excess of alkalinity or acidity. Salvarsan and neosalvarsan treated with fresh rabbit-liver *in vitro* did not acquire a greater toxicity for Leishmania. A dilution of the salvarsanized liver suspen-

[1] I am indebted for these drugs to Dr. Wade H. Brown, of the Rockefeller Institute for Medical Research.

sion corresponding to 1:1,000 of the drug killed the Leishmanias promptly, but not the 1:10,000. It may be recalled here that the original germicidal titre of salvarsan for *Treponema pallidum* (culture) was between 1:1,000, and 1:10,000, but that it rose to 1:100,000 after treatment with fresh rabbit-liver.

As already stated, all the bismuth compounds and several arsenic preparations were insoluble in water, but there was a possibility that some of these drugs might become soluble and reveal their germicidal action when injected into the veins of certain suitable animals — for example, rabbits. Five of the arsenic benzene derivatives might be expected to undergo such a change *in vivo*, since they dissolved *in vitro* upon addition of NaOH in adequate quantities. Each of 24 rabbits received a suspension or solution of one of the 23 substances tested. In the case of tartar emetic and emetine hydrochloride, a 2 per cent aqueous solution was used.

A rabbit weighing 1,900 grams received 8 cc. of 2 per cent tartar emetic solution into the marginal ear vein, and died within 4 minutes after severe reactions. The blood was withdrawn from the heart 9 minutes from the time of injection. A rabbit of 1,550 grams receiving 2 cc. of 2 per cent tartar emetic survived, though reacting severely for several minutes; the blood was collected 1 hour after injection; 2 cc. of a 2 per cent emetine solution were given intravenously to a rabbit weighing 1,800 grams, the animal died within a few minutes, and the blood was taken from the heart.

The serum from the first rabbit had no effect upon Leishmania, but the serum from the second caused a decided slackening of motility in 1:10 dilution; the serum from the third rabbit (emetine) immobilized the organisms in a 1:10 dilution. The 1:10 dilution was chosen for the tests of the drugged serums, because normal rabbit-serum killed Leishmanias when undiluted, but had no effect upon them in a 1:10 dilution.

All the bismuth salts were suspended in saline in concentration of 0.1 gram per 10 cc. of saline, but the quantities injected could not be exactly estimated because of the rapid sedimentation of the insoluble particles while the syringe

was being charged. Each animal received approximately 0.05 grams intravenously, and none died within 1 hour. At the end of this period they were sacrificed, to obtain serum. A slight diminution of motility was noticed when cultures of Leishmania were mixed with the serums derived from rabbits injected with the tartrate and subgallate of bismuth, but no injurious effect was perceptible with the serums from animals receiving the other bismuth compounds. Ten organic compounds of arsenic tested similarly yielded chiefly negative results. Salvarsan and neosalvarsan contained in the serum of rabbits intravenously injected with 0.1 and 0.15 grams respectively, proved to be highly germicidal for *Treponema pallidum* and *Spironema duttoni*, notwithstanding their inertness toward Leishmania, showing their specific affinity for spirochetes.

Sodium oleate and urotropin, 0.1 gram given intravenously to rabbits, did not yield a serum germicidal for Leishmania. The oleate killed the animal in 3 minutes.

The foregoing experiments left the mechanism of the curative effect of antimony treatment in human leishmaniases unsolved. It is striking that tartar emetic and the bismuth compounds are so slightly injurious for Leishmania, either directly or indirectly through the action of fresh tissues or the animal body. A greater germicidal effect on Leishmania was exhibited by salvarsan and neosalvarsan, and was retained after fresh tissues or the animal body had acted upon them, while the spirocheticidal potency of these two drugs was greatly enhanced by passage through the animal body. It seems, therefore, that the curative effects of these compounds in the treatment of human leishmaniases are brought about by a slow transformation of comparatively insoluble substances into a soluble parasiticide in the human body.

Dyes and Photodynamic Sterilization

During the study of various disinfectants, including some of the germicidal dyes, a very striking phenomenon of photodynamic sterilization was encountered. A dye known as neutral acriflavine, or, more simply, "neutroflavine,"[1] a

[1] Made by the National Aniline Company, 40 Rector St., New York City, and sold at a price of $6.00 for 5 grams.

derivative of acid acriflavine (3, 6 diamido 10 methyl acridinium) was found to be markedly germicidal for Leishmania when employed in sufficient concentration, 1:50,000. But beyond a certain point, it was no longer germicidal, yet these higher dilutions exerted a rapid devitalizing effect when the dark-field microscope was used to examine the preparations. A suspension of active Leishmania culture, for example, in a dilution of 1:100,000 of neutroflavine remained unaffected in ordinary diffuse daylight in the laboratory, for many hours; but the moment a slide prepared from the mixture was brought to focus under the dark-field microscope (a Leitz arc-lamp being used), the actively motile flagellates lost their motility instantaneously. The effect was so striking as to suggest the so-called photodynamic action of certain fluorescent dyes, but when actually tested none of the fluorescent photosensitizers, such as erythrosin, eosin, and fluorescein, showed any germicidal property, either with or without the aid of the arc-lamp. Cyanine, a blue sensitizer, showed marked germicidal and photodynamic action somewhat comparable to neutroflavine, but the dye was difficult to work with in this sort of experiment because of its practical insolubility in water. A brief experimental survey of various dyes furnished the following data (Table I).

Of 18 dyes examined, 11 proved to be capable of exerting a photodynamic destructive action upon Leishmanias. In the majority of cases the optimum photodynamic doses were close to the minimum native killing doses[1]. The minimum photodynamic doses, however, were much smaller with certain dyes than with others. In the case of neutroflavine it was 1/2,000 of the native disinfecting dose, while with brilliant green, Janus green, basic fuchsin, tryparosan, pyoktanin blue and pyrrol blue, it was 1/100, and with gentian violet and brilliant blue it was only 1/10. The great native disinfecting power of gentian violet against Leishmania (1:1,000,000) was extraordinary as compared with our everyday disinfectants such as phenol, mercury bichloride, hydrogen peroxide, formalin, and iodine, yet Leishmania is Gram-negative.

[1] In the case of neutroflavine, there is a zone of concentration in which there is no native germicidal effect, yet the dye is too concentrated (perhaps too yellow) to become photodynamically active.

TABLE I

DYES AND PHOTODYNAMIC STERILIZATION

	Native Germicidal Concentration Minimum	Range of Photodynamic Concentrations Optimum	Minimum
Neutroflavine	1:50,000	1:100,000	1:10,000,000
Neutral red	1:50,000	1:100,000	1:1,000,000
Brilliant green	1:100,000	1:1,000,000	1:10,000,000
Janus green	1:100,000	1:1,000,000	1:10,000,000
Gentian violet	1:1,000,000	1:5,000,000	1:10,000,000
Tryparosan	1:10,000	1:100,000	1:1,000,000
Basic fuchsin	1:10,000	1:100,000	1:1,000,000
Acid fuchsin	None at 1:1,000	None at any dilution	
Pyoktanin blue	1:100,000	1:1,000,000	1:10,000,000
Brilliant blue	1:1,000	1:5,000	1:10,000
Pyrrol blue	1:10,000	1:100,000	1:1,000,000
Cyanine	1:50,000	1:100,000	1:1,000,000
Optochin	1:5,000	None at any dilution	
Trypan blue	None at 1:100	None at any dilution	
Trypan red	None at 1:100	None at any dilution	
Scarlet red	None at 1:100	None at any dilution	
Erythrosin	None at 1:100	None at any dilution	
Eosin	None at 1:100	None at any dilution	
Fluorescein	None at 1:100	None at any dilution	
Phenol	1:100	None at any dilution	
$HgCl_2$	1:50,000	None at any dilution	
H_2O_2 (30%)	1:1,000	None at any dilution	
Formalin (40%)	1:1,000	None at any dilution	
Lugol's solution	1:100	None at any dilution	

Whether or not the same atomic groups of a photodynamically active dye are responsible for the native disinfecting action in higher concentrations and the photodynamic effect in greater dilutions, I cannot say, but the following observations seem to have some bearing on the question: — Neutroflavine presents a deep brownish-black color at a 1:100 dilution, a deep brownish-yellow at 1:1,000, a bright orange at 1:10,000, a daffodil-yellow at 1:100,000, a pale lemon at 1:1,000,000, a trace of yellow at 1:10,000,000, and no perceptible color at 1:100,000,000. Solutions of from 1:100 to 1:50,000 concentrations (still bright yellow) kill the flagellates in a laboratory room (diffuse daylight) like any ordinary disinfectant, but those from 1:100,000 to 1:10,000,000 con-

centration (trace of yellow) kill them only in the presence of a powerful light. The 1:100,000,000 dilution is not strong enough to have any action, even in the presence of intense rays. The potentially photodynamic solutions of the dye behave very differently, according to the variety and intensity of the rays used. For example, rays passed through a blue filter kill the Leishmania suspended in a 1:1,000,000 dilution of neutroflavine within 1 to 2 seconds, green rays within 10, and greenish-yellow within about 30 seconds, while rays passed through an orange, yellow, or red filter are without effect.

It is obvious that only rays of shorter wave-length are concerned in this phenomenon. Direct sun's rays applied to a slide preparation of Leishmania suspended in a 1:1,000,000 solution of neutroflavine kills the organisms in about 30 seconds, but by condensation of the rays upon the slide (which is protected from heat by means of cooling devices), killing can be accomplished in a few seconds. Leishmanias in control-slides, minus the dye, stand all these manipulations perfectly well and remain active for a long time. That the acquisition of the anti-Leishmania property by the very high dilutions of neutroflavine was not due to the action of heat, was indirectly shown by the filtered-ray experiments and by the application of various temperatures (26° to 37° C.) in the absence of light. No evidence has been obtained that the formation of a toxic substance from a dilute solution of neutroflavine by the action of actinic rays takes place in the absence of living cells (Leishmania, Treponema, Spironema and Leptospira). The photodynamic action takes place only in a mixture of susceptible organisms and dilute dyes in the presence of sufficiently intense rays.

Neutroflavine is relatively non-toxic for man, has a strong inherent antiseptic property, and, finally, the unusually powerful photodynamic sterilizing quality in a dilution as high as 1:10,000,000 in the presence of actinic rays.

That neutroflavine remains active in the blood for the first 2 hours after its introduction into the general circulation, has been proved in an experiment upon a rabbit. The animal received 10 mg. neutroflavine per kilogram body-weight intravenously, and specimens of the blood were tested after 10,

45, and 75 minutes, after 2 hours, and finally after 20 hours. All specimens except the last, which was without any action, contained enough neutroflavine to tint the citrate plasma yellowish, and revealed a prompt photodynamic action on Leishmania.

Neutroflavine might first be tested for its therapeutic action as an external disinfectant over ulcerated lesions in a 1:1,000 solution, and simultaneously as a local tissue-sterilizer, by injection of a 1:10,000 solution into the lesions, but greater benefit might be derived from its use as an internal (in cases of visceral leishmaniasis) and also as a photodynamic disinfectant. To attain the concentration of 1:50,000 (the minimum native disinfecting dose) of the dye in the general circulation of a person having approximately 6,000 cc. of blood (estimating the blood as 1/13 of 80 kilograms body weight), 0.12 grams of the substance would have to be given intravenously, an amount only ¼ of that which the rabbit tolerated without inconvenience. In Germany neutroflavine has been used in a dose of 0.2 grams at 12-hour intervals (intravenously) in cases of influenza, pneumonia, and septicemia, without any ill effects. Neutroflavine is eliminated through the urine at the rate of 0.2 grams in 36 to 48 hours, according to a report from Germany, where the dye has been used in large quantities for the treatment of acute infections.

X-rays, unlike actinic rays, are unable to convert neutroflavine into a substance toxic for Leishmania, and are themselves inactive toward the organism.

SUMMARY AND DISCUSSION

Leishmania donovani, *L. infantum*, *L. tropica*, and *L. brasiliensis* grow well on a semi-fluid medium described and form a heavy, grayish surface-growth several millimeters in depth. The medium is easily preserved and facilitates maintenance of subcultures, isolation of new strains, and employment of large quantities of the organisms.

All of these strains of Leishmania require oxygen for growth. None was able to grow in an atmosphere of hydrogen, nitrogen, or carbon dioxide

All the strains of Leishmania studied grew well when the

hydrogen ion concentration of the medium was within the range of pH 5.08 to pH 7.21, but *L. tropica* and *L. infantum* grew well up to pH 8.8 and pH 8.19, respectively, while *L. brasiliensis* and *L. donovani* did not grow beyond pH 8.19 and pH 7.21, respectively.

All the strains studied were killed by an alkalinity greater than N/10 NaOH or an acidity greater than N/10 HCl, when the acid or alkali was added to 0.9 per cent NaCl. Distilled water causes immediate disintegration of the flagellates, while a tonicity greater than 0.3 per cent and up to 0.9 per cent NaCl is well borne. The organisms are immobilized by half-saturated saline solution.

Certain phytotoxins and plant toxalbumins kill Leishmania cultures. For example, saponin in a 1:10,000 dilution killed them without dissolution of either the bodies or the flagella. Ricin in a 1:100 dilution caused immobilization and agglutination, but abrin was inactive.

Leishmania was also killed by a number of animal poisons under certain conditions. The venom of the Indian cobra affected them in a 1:2,000 dilution in 0.9 per cent NaCl and killed in a 1:20,000 dilution when a small amount of lecithin (otherwise harmless) was added. Solutions in saline (1:200) of the venoms of *Lachesis lanceolatus*, *L. flavoviridis*, *Ancistrodon piscivorus* (water moccasin), *Crotalus adamanteus* (diamond-back rattlesnake of Florida), *Vipera russelli* (Indian daboia), and a Japanese viper (*mamushi*) had no effect upon Leishmania *in vitro*. In the presence of lecithin, however, the venoms of Lachesis and Ancistrodon exerted a slight lytic effect, but those of the rattlesnake and *mamushi* remained inactive.

By means of monovalent immune serums produced in rabbits it was possible to differentiate, through agglutination tests, and cultivation on media containing immune serums, *Leishmania donovani* from *L. tropica* or *L. brasiliensis*, each of these strains representing a serologically independent and distinct unit. *L. infantum* was found to be serologically identical with, or closely allied to, *L. donovani*. These findings conform with the clinical observations, which indicate that the visceral leishmaniases (*L. donovani* and *L. infantum*) are distinct from the benign oriental sore

(*L. tropica*), which is merely a skin infection, and probably also from the American type of leishmaniasis (*L. brasiliensis*), which involves both skin and mucous membranes and is often malignant. This distinction may prove useful in the utilization of immunity phenomena in connection with prophylactic and therapeutic measures.

Attempts were made to determine the mechanism by which tartar emetic acts to effect a cure in leishmaniasis. The antimony compound was found to be only slightly germicidal for Leishmanias *in vitro*, a 1:100 solution being required to kill them. Brief contact with fresh animal-tissues, or intravenous introduction into rabbits, did not transform this substance into a more potent germicide for these organisms. Hence the exact mode of action of the drug upon the parasites in human leishmaniasis has not been explained.

Salvarsan, sometimes reported to have cured leishmaniasis, and also neosalvarsan, have been similarly studied, and both showed a native disinfecting power nearly 10 times as great as that of tartar emetic. A 1:1,000 solution of salvarsan killed the Leishmanias in saline solution, and both arsenical compounds retained their germicidal powers after having been emulsified with a fragment of fresh rabbit-liver or subjected to the action of the animal body by means of intravenous inoculation into rabbits. These procedures, however, greatly enhanced the germicidal power of these two drugs for *Treponema pallidum* and *Spironema duttoni*.

Several other organic compounds of arsenic and bismuth have been studied in the same way, but the results were even less informing. Bismuth tartrate seemed to acquire slight leishmanicidal power after treatment with fresh tissues or injection into the animal body.

The photodynamic properties of certain fluorescent dyes have long been known, and fluorescence and photodynamic action were thought to be closely associated. In the present study, however, a peculiar phenomenon was observed, in which flagellates and spirochetes were rapidly killed by extraordinarily dilute, and otherwise inactive, solutions of certain germicidal dyes in the presence of actinic rays. Neither the solutions nor the rays alone harmed the organisms, and the dyes did not seem to have been converted into

a germicide of greater potency, since solutions exposed to the rays without the simultaneous presence of the micro-organisms did not become germicidal.

The occurrence of the phenomenon required the simultaneous presence of the dye in high dilutions, the micro-organisms, and actinic rays, and is therefore somewhat different from the so-called photodynamic action of certain fluorescent dyes in which the formation of peroxide in the presence of ordinary light is said to play a part. The phenomenon does not occur with any of the well-known photodynamic fluorescent dyes — eosin, erythrosin, and fluorescein — none of which was either inherently or photodynamically germicidal for the flagellates. Eleven of 18 dyes, chiefly non-fluorescent, were found to possess native, as well as photodynamic, germicidal properties. The most striking example of the group is neutral acriflavine or neutroflavine, which killed Leishmania, Treponema, Spironema, and Leptospira in a dilution of 1:50,000 without the aid of a special light, and in a dilution of 1:10,000,000 with the aid of actinic rays. An arc-lamp or the sun's rays furnish all the actinic energy required for this action. Rays filtered through a red, orange, or yellow screen exert no photodynamic action upon the dye solution, but those passed through a blue filter act most energetically.

The fact that neutroflavine is well tolerated by man, remains in the circulation active for many hours, possesses a strong inherent antiseptic property and, above all, the unusually powerful photodynamic sterilizing quality in a dilution as high as 1:10,000,000, makes it highly promising as an agent for the treatment of certain protozoan diseases associated with chronic ulcers. Leishmaniasis and various forms of spirochetosis offer a wide field for testing out the sterilizing effect of this and allied dyes in tropical regions.

ADDENDUM

PLANT FLAGELLATES AND LEISHMANIA

The various skin ulcers of Brazil, particularly those of the Brazilian type of leishmaniasis, are said to be very common among persons who are engaged in clearing uncultivated woodlands, and the possibility suggests itself of demonstrat-

ing the pathogenic Leishmania in plants. A great deal of investigation[1] regarding the natural reservoirs of Leishmania in plants and invertebrates has already been carried out by Lafont, França, Laveran and Franchini, Rhodain and Bequaert, Noc and Stévenel, Léger, Migone, Fantham, Hoare, Glaser, and Becker, but there have been only occasional successes in transmitting the flagellates of plants or insects to a mammalian host. Strong[2], in a recent important contribution to this subject, reports that he has found flagellates morphologically identical in the latex of Euphorbia, in a hemipteran insect feeding upon the plants, and in the intestine of a lizard probably feeding on the insects, and that he has succeeded in producing a skin ulcer in a monkey by injection of flagellate-containing intestinal contents of the lizard. Non-flagellated forms of the protozoön were found in the granulomatous tissues at the site of the ulcer, forms morphologically similar to the aflagellate form of Leishmania.

During my brief sojourn in Kingston, while attending the present Conference, I had the good fortune to meet several investigators who, like myself, were interested in plant flagellates, and through the kind advice of Dr. Juan Iturbe, of Caracas, Venezuela, and Dr. R. W. Hegner, of Johns Hopkins University, I was able to begin a brief study, the results of which follow. My interest in this subject was limited to obtaining the flagellates in culture, if possible, and comparing their morphological, biological, and immunological properties.

Two varieties of Euphorbia found in Kingston (*E. pilulifera* and *E. maculata* (?)) and about a dozen latex plants in the Hope Botanical Garden[3] were examined, with negative

[1] LAFONT, A.; *Bull. Soc. Path. Exot.*, 1911, iv, 464. FRANÇA, C., *Arch. f. Protistenk.*, 1914, xxxiv, 108; *Bull. Soc. Path. Exot.*, 1911, iv, 532; 669; *Ann. de l'Inst. Pasteur*, 1920, xxxiv, 432. LAVERAN, A., and FRANCHINI, G.; *Bull. Soc. Path. Exot.*, 1921, xiv, 148. RHODAIN, J., and BEQUAERT J.,; *Bull. Soc. Path. Exot.*, 1911, iv, 198. NOC, F., and STÉVENEL, L.; *Bull. Soc. Path. Exot.*, 1911, iv, 461. LÉGER, A.; *Bull. Soc. Path. Exot.*, 1911, iv, 626. MIGONE, L. E.; *Bull. Soc. Path. Exot.*, 1916, ix, 356. FANTHAM, H. B.; *Ann. Trop. Med. and Parasitol.*, 1915, ix, 341; *S. African Journ. Sci.*, 1922, xix, 332. HOARE, C. A ; *Parasitology*, 1921, xiii, 67. GLASER, M.; *Journ. Parasitol*, 1922, viii, 99. BECKER, E. R.; *Amer. Journ. Hyg.*, 1923, iii, 462.

[2] STRONG, R. P.; *Am. Journ. Trop. Med.*, 1924, iv, 345.

[3] For the use of the dark-field microscope, I am indebted to Drs. MacLean and Moody, of Kingston.

results[1]. The search was renewed in Tela, Honduras, where Strong had recently demonstrated flagellates in *Euphorbia pilulifera* and Hegner in *Asclepias curassavica*, and with the help of Dr. Herbert C. Clark, of Tela Hospital I was able to obtain material for study. Among about 50 milkweeds (*Asclepias curassavica*) (Figs. 9, 10) flagellates were found in the latex of 2; and of nearly 100 *E. pilulifera*, and *E.* (*Chamaesyce*) *brasiliensis* (Fig. 11)[2] only 1 of the former and 2 of the latter proved to be infected. In accordance with Hegner's previous observation, the older Asclepias with pods were the ones infected, and in the case of Euphorbia, the flagellates were found in old, sickly-looking specimens, as recorded by Lafont, França, and Strong. A number of specimens of the creeping variety of Euphorbia (*E. maculata* (?)) were examined, with negative results.

In all of the 5 positive plants, the infection was confined to certain stems or branches; for example, only 1 of 2 collateral branches would contain the flagellates. The number of organisms present in the infected latex is astonishingly large, each field (objective 2 mm. and ocular K.8) revealing a dozen or more actively motile organisms.

As also observed recently by Holmes[3], the American milkweed, *Asclepias syriaca* (probably *syriaca*) also occasionally harbors a flagellate of the herpetomonad type. Several infected plants have been encountered among several hundred examined on Long Island, N. Y.

On the flowers and pods of *Asclepias curassavica* were found numerous nymphs and winged adults of a hemipteran insect, later identified by Dr. H. G. Barber, of the American Museum of Natural History, as *Oncopeltus cingulifer* (Fig. 12). Six of the nymphs brought back from Honduras were dissected at the Rockefeller Institute by Miss Tilden, who found numerous herpetomonads in the intestines of 3 of them. Four adults, 1 male and 3 females, were placed in a cage on a group of the *Asclepias curassavica* in a greenhouse (80° F.);

[1] About 50 specimens of Euphorbia, collected in the suburbs of Havana and on the grounds of Las Animas Hospital on the occasion of my visit to Dr. Lebredo, the Director, and brought back to New York, were also negative.

[2] For identification of these specimens of Euphorbia (Chamaesyce) I am indebted to Dr. H. A. Gleason, of the New York Botanical Garden, Bronx Park.

[3] HOLMES, F. O.; *Phytopathology*, 1924, xiv, 146.

2 weeks later a cluster of 80 salmon-pink eggs (about 0.8 mm. in diameter) were found in a crevice of the cage. These hatched 4 days later, and in 3 weeks the nymphs passed through several moultings and attained a size of about 5 mm. Five of these were examined at this period, but in only 1 was the herpetomonad found. Later on, however, practically all were found to be infected with the herpetomonad. The plants upon which the adults and young nymphs have been feeding for more than 3 months have gradually lost most of their young leaves but repeated examinations of leaves from these plants has so far failed to show that the latex is infected with flagellates.

Morphology of the Flagellates

In a freshly prepared slide, as seen by dark-field illumination, the plant forms are rather sluggishly motile, and many of them are provided with a flagellum. The body is an elongated, thin, lanceolate form with smooth contour, narrowing at both extremities to a point; one end is somewhat less pointed than the other, and the flagellum is attached at this end. From the posterior end a thin tremulous filament is often seen, which appears as if it were drawn out of some viscid substance such as mucin. The flagellum moves in a wriggling or jerking fashion, drawing the otherwise immotile body forward. The comparative shortness of the flagellum and the flattened body are in striking contrast to the usual culture forms of various strains of Leishmania, as seen by dark-field illumination.

At the end of about an hour the number of motile forms in the preparation becomes fewer, and there appear a great many immotile organisms devoid of flagella, which tend to twist spirally once, twice, or even half a turn more. Occasionally these forms are seen in fresh preparations.

Stained with Giemsa's or Wright's solution, the herpetomonad from *Asclepias curassavica* (Fig. 6) is shown to have an oblong or round nucleus and a short, rod-shaped parabasal body transverse to the axis of the body, and close to the attachment of the flagellum. The organism is somewhat shorter and broader than the one found in *Euphorbia brasiliensis* (Fig. 5) the length varying from 14 to 20 μ, and the width from 2 to 4 μ, as compared with a length of 17 to 30 μ

and a width of 1.4 to 2 μ for the Euphorbia organism. The distance between parabasal body and nucleus is also less, averaging 1.9 μ as compared with 3.8 μ. In the Euphorbia flagellate the parabasal body is round. The flagellate found in *Asclepias syriaca* (Fig. 7) is very similar to that of *A. curassavica.*

The herpetomonad found in the intestine of *Oncopeltus cingulifer* (Fig. 8) as seen by dark-field examination, is more actively motile than those of the plant latex. The long flagellum — its length usually exceeds that of the body — moves in a serpentine fashion. The body is somewhat longer and thicker, and shows less tendency to spiral twisting, and the cytoplasm contains a number of highly refractile granules, rarely seen in the plant forms. In preparations stained with Giemsa's solution the length of the body varies from 18 to 28 μ, average 24 μ, the width at the widest portion being 1.8 to 3.5 μ, and the distance from parabasal body to nucleus 3μ. The parabasal body is round and measures about 1 μ in diameter.

There is little or no difficulty, either in fresh or stained preparations, in distinguishing the insect from the plant forms. Some specimens of the herpetomonad forms of Leishmania, grown on leptospira medium, are very similar to the insect forms, but in general the Leishmania flagellates (Figs. 1–4) are shorter and have a thicker, and often broader, body. In the culture forms of Leishmania, moreover, the length of the flagellum rarely exceeds that of the body, and in pyriform specimens the nucleus is situated near the posterior end of the body. For comparison there are recorded here the measurements of the plant and insect forms. Attempts were made to record similar measurements for Leishmania, but the dimensions of the multiplying culture forms vary greatly, not only in cultures of different ages, but in the same culture, while those of the insect and plant forms are fairly constant; hence the measurements would not be comparable.

TABLE 2

HERPETOMONADS FROM ASCLEPIAS CURASSAVICA

	Length of Body	Anterior End to Parabasal Body	Parabasal Body to Nucleus	Nucleus	Posterior End to Nucleus	Width at Widest Portion	Length of Flagellum
Methyl alcohol fixation	20 μ	2 μ	1.8 μ	2.8 μ	13 μ	3 μ	5 μ
	19	1.8	1.6	3	13	4	
	17	2	1.5	3.2	10	2.5	2
	17	1.8	2.2	2.5	10	2.8	
	15	1.2	1.5	2.5	9	3	
	16	1.5	2	2.2	9	3	
	20	1.6	2	2.5	14	2.5	
	15	1.8	1.4	2.2	9	3	
	16	1.5	2	2	10	2.5	
	20	1.8	2	3	13	2.8	
	15	1.2	1.8	2.2	9	2.6	
	20	1.5	1.7	2.5	14	2.8	
	15.2	1.5	1.5	2.1	10	2.3	
	17	1.5	1.5	1.5	12	2.3	
	20	2	1.8	2.6	12	2.4	3
	20	2	1.8	2.5	13.5	4	12
	18	2	1.5	3	11	3	
S. A. fixation	17	1.8	1.5	3	10	3	
	16	1.5	1.3	2.5	10	3	7
	16	1.8	2	2.6	9.4	2.5	9
	14	1.5	1.5	2	9	2	3
	16	1.5	4	2	8.5	2	
	16	1.5	4	2.5	8	2.2	
	17	1.5	2.5	2	11	2	
	17	1.5	2.5	2.5	10.5	2.1	
Range	14-20 μ	1.2-2 μ	1.3-4 μ	2-3 μ	8-14 μ	2-4 μ	3-12 μ
Average	17.5 μ	1.7 μ	1.9 μ	2.5 μ	10.7 μ	2.7 μ	

TABLE 3

HERPETOMONADS FROM EUPHORBIA BRASILIENSIS

Length of Body	Anterior End to Parabasal Body	Parabasal Body to Nucleus	Nucleus	Posterior End to Nucleus	Width at Widest Portion	Length of Flagellum
24 μ	2 μ	4 μ	3 μ	14 μ	1.5 μ	10 μ
21	1.8	2.2	2	14	1.8	12
17	1.6	2.5	2.2	11.3	1.4	12
24	1.8	2.1	2.5	17.6	1.8	12
19	1.8	2	2	13.2	1.8	12
28	1.5	4	2	20	1.8	15
22	1.5	5	2.2	13.3	1.8	12
22	1.5	5	2.2	13.3	1.8	10
30	2	4	3	21	2	15
25.2	2	5	2.2	16	2	14
30	1.8	6	3	19.2	2	14
Range 17-30 μ	1.5-2 μ	2-6 μ	2-3 μ	11.3-21 μ	1.4-2 μ	10-15 μ
Average 23.8 μ	1.75 μ	3.8 μ	2.4 μ	15.7 μ	1.8 μ	12.5 μ

TABLE 4

HERPETOMONADS FROM ASCLEPIAS SYRIACA

Length of Body	Anterior End to Parabasal Body	Parabasal Body to Nucleus	Nucleus	Posterior End to Nucleus	Width at Widest Portion	Length of Flagellum
18.5 μ	2 μ	4 μ	2.5 μ	10 μ	2.2 μ	8 μ
14	1.8	4	2.2	6	2.2	8
16	2	3	2	9	2.2	10
18	2	4	2.2	10	2.5	10
18	2	3.5	2.3	11	3	10
17	2	3	2.2	10	3.5	10
20	1.8	2.5	3	12	2.5	10
20	2	4	2.5	11	2.5	12
16	1.8	4	2.1	8	2.8	8
18	1.8	2.2	2.2	12	2.5	10
22	2	2.5	3	14.5	3	12
13	1.8	2.5	2.8	5	2.5	6
15.5	2	3.5	3	7	2.2	12
13	2	2	3	6	3.2	6
14	1.8	4	3	6	3.5	9
22	2	5	3	12	2.2	12
11	1.5	2.2	2.2	5	2	6
20	2	1.2	2.2	12.5	2.5	6
16	1.8	2	2.5	10	2	8
16	1.8	2.2	2.2	10	2.5	12
Range 13-22 μ	1.5-2 μ	1.2-5 μ	2-3 μ	5-14.5 μ	2-3.5 μ	6-12 μ
Average 16 μ	1.9 μ	2.8 μ	2.5 μ	9 μ	2.3 μ	8.8 μ

TABLE 5

HERPETOMONADS FROM ONCOPELTUS CINGULIFER

Length of Body	Anterior End to Parabasal Body	Parabasal Body to Nucleus	Nucleus	Posterior End to Nucleus	Width at Widest Portion	Length of Flagellum
25 μ	4 μ	3 μ	3 μ	15 μ	3.5 μ	28 μ
24	4	3	3	14	3	25
18	2	3	2.5	7	2	18

Whether or not the herpetomonads found in the latex plants and in the hemipteran insects associated with them are identical, and only modified by the difference in hosts, or represent more than one species, as would appear from purely morphological features, is yet to be determined.

Cultivation

The facility with which a strain of human Leishmania can be cultivated in the semi-fluid leptospira medium, led to its being the first tried for the cultivation of the plant flagellates. Both human and rabbit serum and hemoglobin were alternately used in its preparation. In addition to the usual medium with alkaline reaction (pH 7.5), media adjusted to various degrees of alkalinity and acidity were employed, including one made acid to a degree approximating the reaction of the latex of Asclepias and Euphorbia. The addition of N/10 HCl in quantities greater than 0.3 cc. to 8 cc. of the regular leptospira medium causes opalescence and finally heavy precipitation of the serum constituents. Fresh and also autoclaved coconut milk, the acidity of which is approximately the same as the plant latex, were used both with and without the addition of serum, hemoglobin, or agar. The regular N.N.N. blood agar slant was also tried. The inoculum consisted of the fresh latex, which oozes out when a leaf is broken off. Bacterial contamination almost invariably followed the use of undiluted latex, but when the latex was diluted 1:10 or 1:20 with sterile saline or Ringer-Tyrode not containing bicarbonate, the frequency of bacterial contamination was greatly reduced. Cultivation was carried out at laboratory temperature in Tela, the cultures were kept in the steamer cabin during the trip from Honduras to New York, and the temperature has not exceeded 35° C. at any time.

No culture of the plant flagellates has thus far been obtained. The longest survival was 12 days on the leptospira medium, but with no indication of multiplication. On the other hand, cultures of *L. tropica* and *L. brasiliensis* grew luxuriantly, under the same conditions, on the leptospira medium and also on the N.N.N. medium.

Attempts to cultivate the herpetomonads of *Oncopeltus cingulifer* have likewise been fruitless. It is evident, therefore, that the cultural requirements of the plant and insect flagellates studied are quite different from those of Leishmania.

Effects of Anti-Leishmania Immune Serums upon the Plant and Insect Flagellates

Although cultures could not be obtained, the latices of the plants and the intestinal contents of *Oncopeltus cingulifer* constituted natural cultures, owing to the extremely large numbers of the motile flagellates present. It appeared feasible, therefore, to utilize these materials to determine the action of the immune serums of high titre which had been produced by immunization of rabbits against the various strains of Leishmania. Four types of immune serums were used, anti-*brasiliensis*, anti-*tropica*, anti-*infantum*, and anti-*donovani*.

The results of this experiment were decisive, inasmuch as neither the plant nor the insect flagellates were influenced by the addition of any of the 4 anti-Leishmania immune serums, their motility and form remaining unchanged even in dilutions of 1:2 and 1:20. There was a phenomenon of agglomeration, but it occurred also in controls with normal rabbit-serum. On the other hand, these immune serums caused rapid agglutination of their homologous strains of Leishmania culture forms into enormous masses of distorted organisms with swollen flagella. This specific agglutination cannot be confused with the non-specific agglomeration so frequently observed with various flagellates.

It would appear, therefore, that the flagellates as they exist in the latex of *A. curassavica*, *A. syriaca*, or *E. brasiliensis*, or in the intestine of *Oncopeltus cingulifer* are immunologically distinct from the four strains of human Leishmania. The differences in immune reactions, as well as in cultural

properties, between the plant or insect flagellates and human Leishmania may well be an expression of faculties acquired under highly specialized environments. It is also possible that there may exist, among the flagellates in these latex plants, or hemipterans, certain strains which are immunologically and culturally identical with the Leishmania from human sources and are capable of producing the skin infection in man, either directly or after gradual adaptation through insects and lizards, as postulated by Strong.

I wish to thank Dr. Deeks for his courtesy in according me the privilege of working at the Tela Hospital during part of this experimentation, and Dr. Nutter and his associates at the hospital, Dr. Roberts and Dr. Muldoon, for their hospitality during my visit. As already stated, I am indebted to Dr. Hegner and Dr. Iturbe for having given me the benefit of their knowledge, and to Dr. Herbert C. Clark, the Director of the Laboratory of Tela Hospital, for constant coöperation and attention.

EXPLANATION OF PLATES

PLATE A. Gross appearance of Leishmania cultures grown on media containing either homologous or heterologous immune rabbit serums. The growth is granular or clumpy in homologous, but smooth in heterologous immune serum media. The age of the cultures was 30 days at room temperature (18° C.).

All specimens shown in Figs. 1-8 were stained with Giemsa's solution and magnified x1250 diameters.

FIG. 1. Culture forms of *Leishmania tropica*, grown 11 days at 18° C. on the leptospira medium.

FIGS. 2, 3, and 4 represent, respectively, culture forms of *L. brasiliensis*, *L. infantum*, and *L. donovani*, grown under the same conditions.

FIG. 5. Herpetomonads from the latex of *Euphorbia brasiliensis* from Tela, Honduras.

FIG. 6. Herpetomonads from the latex of *Asclepias curassavica* (Tela, Honduras). At the lower, right side a human erythrocyte is shown for comparison.

FIG. 7. Herpetomonads from the latex of *Asclepias syriaca* (Long Island, New York).

FIG. 8. Herpetomonads from the intestine of *Oncopeltus cingulifer*.

FIG. 9. A shoot of *Asclepias curassavica* from Tela, Honduras. Natural size.

FIG. 10. A portion of the stem of the same plant. Natural size.

FIG. 11. A branch of *Euphorbia brasiliensis* from Tela, Honduras. Natural size.

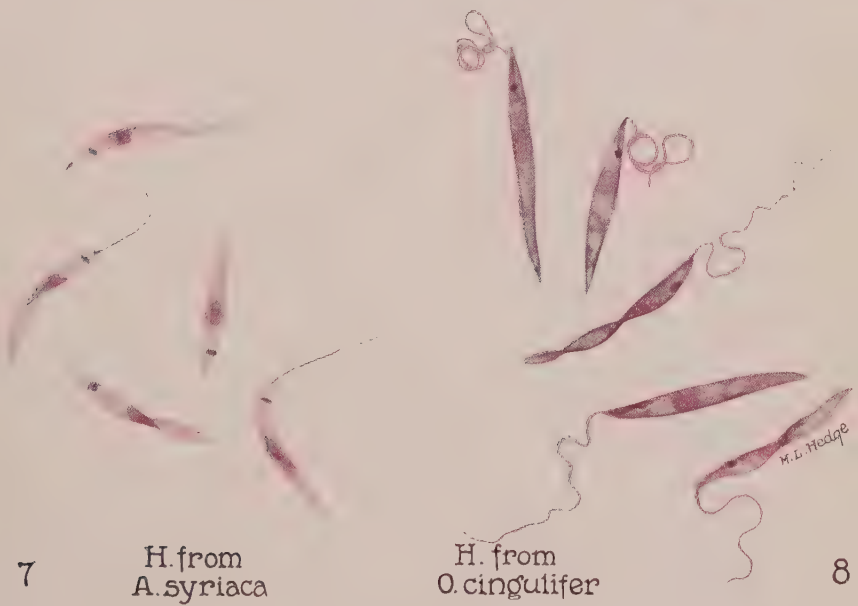
FIG. 12. Dorsal and ventral aspects of male and female of *Oncopeltus cingulifer*. Natural size.

PLATE A. IMMUNOLOGICAL DIFFERENTIATION OF LEISHMANIA IN CULTURE

Plate I. Culture Forms of Leishmania

5 Herpetomonads from E. braziliensis

H. from A. curassavica 6



7 H. from A. syriaca

H. from O. cingulifer 8

PLATE II. PLANT AND INSECT HERPETOMONADS

PLATE III. PLANT AND INSECT HOSTS OF HERPETOMONADS

Discussion

Dr. Aldo Castellani (Opening the Discussion). — Dr. Noguchi has given us a most remarkable résumé of his wonderful work on yellow fever, and on Oriental Sore as found in South and Central America. I shall not touch upon the yellow fever work, however, because I have never carried out any original investigation of the subject. I am very much interested in his researches on the dermal leishmaniasis of Brazil. His investigations have cleared a highly important point, as they have shown that the Brazilian leishmania is different from *L. tropica.*

We all know that when dermal leishmaniasis was found in South America, specimens were sent to Laveran, in Paris, and he and Dr. Nattan Larrier came to the conclusion that the species of Leishmania found in South America was probably a variety of *L. tropica,* and they called it *L. tropica* var. *Americana.* It is well known, however, that the Laveran theory was not accepted generally; in fact, recently there has been a general tendency to consider the parasite of South America as being absolutely identical with the parasite found in Oriental Sore of Asia and Europe.

Noguchi has also shown that the Leishmanias found in dermal conditions are different from the Leishmania of Kala azar, and the old theory which from time to time is revived, to the effect that Oriental Sore is merely a local manifestation of Kala azar, has been completely disproved.

In conclusion, I should like to express again to Dr. Noguchi my profound admiration for his most interesting and important researches.

Dr. Charles A. Kofoid (Closing the Discussion). — I will state very briefly a few facts, some of which have been published by Mrs. Wagener from our laboratories in Berkeley, on intradermal tests on *Leishmania.* Mrs. Wagener has been able in rabbits immunized against both *Leishmania infantum* and *Leishmania tropica* to get distinct intradermal reactions for the two species. These reactions were at all times more pronounced for *L. tropica* than for *L. infantum.* This has recently been repeated, on the same scale, in the white guinea pig. The characteristic differences between the two species are present in both experimentally tested animals. We are indebted to Dr. Nicolle in Tunis, to Dr. Novy in Michigan, to Dr. Tyzzer at Harvard, and to Dr. Young in Peking for the cultures of Leishmania. There are some indications that the species in Peking is immunologically more closely related to the Novy strain of *infantum* than to the strain of this species obtained from Dr. Nicolle.

THE TREATMENT OF ORIENTAL SORE BY MEANS OF PHOSPHORUS

Aldo Castellani, M.D.

My object in reading this brief note is to bring to your notice a new treatment for Oriental Sore which I devised two years ago. The drug used is phosphorus in the form of the ordinary phosphorus oil of the British Pharmacopeia. The treatment is carried out as follows:

1. If the lesion or lesions should be extensively ulcerated, the oil is simply applied, by means of a swab, to the fundus and margins of the sore, — once every day at first, then every 2 or 3 days. The application of the oil is practically painless, and there is no local reaction to speak of, nor general reaction.

2. The nodule is not ulcerated, or only slightly so. In such cases, in addition to the external application, a few minims of the oil (3 to 5) are injected under the skin around the nodule, and also at times deep into the nodule itself, once or twice a week, according to the reaction produced.

The technique of the subcutaneous administration is as follows:

A sterile 20-minim all-glass hypodermic syringe is used; 5 minims of the oil are drawn in and injected in 2 or 3 places under the skin around the nodule, and also into the nodule itself. The subcutaneous injection is practically painless and there is hardly any reaction. The intranodular injection is much more painful, and at times there is a severe local reaction which subsides on boric-acid fomentation.

Cases Treated

Seven cases had been treated with satisfactory results up to the date of my leaving London. An apparently complete cure took place in all of them within a period of 3 weeks to 3 months.

Illustrative cases. Mr. N. D., a young Englishman,

contracted Oriental Sore at Delhi, India. He was treated by means of a prolonged course of tartar-emetic injections. The sore healed, but broke out again 2 weeks after termination of the course. He was then given another course of injections with no appreciable results and was sent home as an untractable case. In London he received again a large number of tartar-emetic injections, and also salvarsan and neo-salvarsan with no benefit. When he came to see me he had a rather large, somewhat shallow ulcer situated in the malar region and near the ear. A microscopical examination for Leishmania was made with positive results. I decided to try the phosphorus treatment, and had him admitted to the Italian Hospital. Phosphorated oil was applied to the ulcer every other day. To my surprise the ulcer healed in 2 weeks.

REMARKS

It must be kept in mind that phosphorus is a powerful poison, and also that it has often a delayed action on the liver. If it is used in the doses I have recommended, however, there is no danger. I may add that although I have used phosphorus in Oriental Sore only during the last 2 years, I used it several years ago in various conditions, such as osteomalacia and rickets, and also as an adjuvant to quinine and arsenic in chronic malaria, since I noticed that the hypodermic injection of phosphorus oil is practically painless.

In conclusion, I should like to emphasize that I do not claim that phosphorus is a specific for *Leishmaniasis*. The good results which I have obtained may have been a coincidence. I merely suggest that it should be tried on a large scale to see whether it is really efficacious or not. I would suggest also that it might be tried on certain non-Leishmanial conditions such as *granuloma inguinale*, *ulcus tropicum*, and *ulcerated tropical rhinoscleroma*.

LITERATURE

CASTELLANI: *British Medical Journal*, February 17, 1923.
CASTELLANI: *Journal of Tropical Medicine*, June 1, 1923.

DISCUSSION

Dr. J. W. W. Stephens (*Opening the Discussion*).—After congratulating Dr. Castellani on adding one more to the very numerous drugs that are being used or have been used in the treatment of Tropical Sore, Dr. Stephens spoke as follows:

In Laveran's book "*Leishmanioses*" the treatments cover some pages, and that I regard as fairly good evidence that none of them are specific. Whether we have any specific drugs I suppose is questionable, but at any rate they are not specific in the sense that we can be certain of "cure" of a fairly large percentage. We should, I think, bear in mind the point that Tropical Sore frequently cures itself, in 6 months to 1 year.

I saw a case some little time ago which had been diagnosed as rodent ulcer. I found the parasites, but observed that there was an edge of fresh epithelium extending inwards. I came to the conclusion that I should be justified in recommending the patient to have nothing done, and events proved I *was* justified, as the sore completely healed in about 1 month. Whether, however, the cure would have been more rapid if I had injected, say, emetine or tried any other of the treatments that are recommended, is a matter of debate. It is necessary to determine whether phosphorus ointment is any better than the numerous ointments we have at the present time. One point which is obscure in the treatment is this, that some observers record extremely good results from intravenous injections of tartar emetic, and others disappointing results.

Dr. James Cran.—Dr. Cran stated that about a year ago a case of a white man came in from the Bush with a very large Oriental Sore which covered almost the whole of the back of the wrist, and part of the hand. The Doctor tried emetine with good results, which, however, were only temporary. He then tried a treatment which he had seen recommended in the *British Medical Journal*, namely, a thorough scraping of the sore under local anæsthesia, and the application of caustic potash. The sore healed up in 2 or 3 weeks, and since that time, under this treatment Dr. Cran said he had had good results with other cases.

Dr. Henry Rose Carter.—I wonder whether Dr. Castellani appreciates what a benefit he may have just conferred on us Americans; or how much more injurious the cutaneous manifestation of *Leishmaniasis* frequently is in the Americas than in the Old World?

In much of the Brazils — I think in all of the *Selva*, the wooded part of the country — and in part of Peru east of the Cordilleras — the *Oriente* of that country — there is a form of *Leishmaniasis*

known as "*espundia.*" I first saw in 1904, in Lima, a case of this; it came from the *Oriente* of Peru. And in 1916, in Bahia, I saw between 40 and 50 cases in the hospital there.

Unlike the Oriental Sore of the eastern Mediterranean and nearby countries — the so-called "Aleppo bouton"— this is a systemic disease. Possibly not in the very beginning, but it soon becomes so; the primary sore apparently acting like the chancre in syphilis.

The condition at Bahia seemed to be this: A lesion appears on some exposed part of the body, exhibiting the usual phenomena of the Aleppo bouton and showing the Leishman-Donovan bodies. A large number — about 40% to 50%, it was judged — followed the usual course of that lesion, but the men in whom the remainder occurred after a lapse of time measured in weeks or months, showed evidences of systemic infection: sometimes by the development of other lesions of the same character. I have seen as many as 6 or 8 of such secondary *boutons* on one man, frequently symmetrical — and *always* (after such development of secondary lesions or without their appearance) accompanied by a swelling in the roof of the mouth, which involved and ultimately, if untreated, destroyed both bones and soft parts and threw the cavities of the mouth and nose into one, producing horrible deformity, or even death.

As I said, only a part of the Leishmania sores at Bahia — 40% to 50% roughly, I was told—were followed by the development of the lesions in the mouth (*espundia*). And the same was true, I was told, at some other coast cities. Up the Amazon, however, the development of *espundia* following the appearance of the "*ferida brava*" (the "savage wound"), as the *bouton* was there called, was regarded as inevitable. The same was stated, by Dr. de Sousa, of Sao Paulo, to be the case in the forest (Selva) of Brazil next to the Paraguay border; and elsewhere in back country in Brazil, as stated by Drs. Torres, Cerquiero and others of Bahia. Only in the coast cities did I hear of a considerable proportion of these boutons occurring and not being followed by *espundia.*

The explanation which at once suggests itself is, that there were 2 distinct forms of *Leishmaniasis* in Brazil: One, native to it (*espundia*) and, because native, showing everywhere in the Selva; and one introduced from the eastern Mediterranean, by the immigrants therefrom, and as yet restricted principally to the coast towns to which at that time such immigrants, Syrians, were mainly (I understood almost entirely) confined. Both showed the Leishmania bodies, and no differences — morpho-

logical or cultural — were observable between those from *espundia* and those from the simple *bouton*.

As possibly bearing on its method of propagation, it was noted that practically all of the cases of *espundia* in Bahia came from the spurs of the city, on ridges running between ravines which were rather densely wooded.

Dr. Aldo Castellani (*Closing the Discussion of his own Paper*).— I am in complete agreement with Professor Stephens, that one must be extremely careful before coming to the conclusion that a new specific treatment has been found for any given disease. I was very much interested in the remarks made by Dr. Carter. His observation that there are 2 types of dermal *Leishmaniasis* in South America,— one imported, the other local, is of great importance. I should like to respectfully congratulate Dr. Carter on the wonderful work which he carried out in South America, and which places him among the great pioneers of modern tropical medicine.

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TROPICAL DERMATOLOGY

ALDO CASTELLANI, M.D.

Tropical dermatology, *sensu strictu*, that is to say without including in it systemic diseases such as leprosy, yaws, pellagra, filariasis, etc., has, comparatively speaking, attracted little attention so far. The subject, however, is of importance from a practical point of view.

Tropical skin diseases may be classified as follows:

(A) Due to vegetal organisms { 1. Bacteria / 2. Fungi
(B) Due to animal organisms { 1. Protozoa / 2. Metazoa
(C) Due to physical and chemical causes.
(D) Of unknown or doubtful origin.

The subject is a very large one, and I will limit myself therefore to saying a few words on some of the less-known skin diseases on which I have carried out certain investigations:

Aspergillosis and Penicilliosis of the beard
Trichomycosis axillaris flava, rubra and *nigra*
Cryptococcosis epidermica
Tinea flava
Tinea nigra
Dermatitis interdigitalis pedum
Tinea imbricata
Pruritus ani of mycotic origin
Little-known pigmentary diseases and other distrophies

Aspergillosis and Penicilliosis OF THE BEARD

The hairs of the beard and mustache are covered with minute, dark-grayish, or black, or greenish nodules, which on microscopical examination are seen to consist of mycelium and fructifications of an aspergillar or penicilliar type. I saw the first case in Equatorial Africa, in 1902, in an Indian merchant; later Chalmers and I came across several cases

in Ceylon. The simplest treatment consists, of course, in shaving, but if the patient objects to it, turpentine and diluted formalin will be found useful.

Trichomycosis Axillaris Flava, Rubra AND *Nigra*

This condition has been partially known for many years under the term *Lepothrix*, but the various types of it were not differentiated, and nothing definite was known about the ætiology, the affection being ascribed to the most diverse germs. Eisner, for instance, considered it to be caused by a diplococcus; Payne, Patterson and Peck inculpated various bacilli, including *B. prodigiosus*.

The condition is characterized by the presence, on the hairs of the axillary regions and occasionally the pubes, of small nodular formations which, from my experience, may be *yellow* or *red* or *black*. I therefore differentiated 3 varieties of the condition—*Trichomycosis axillaris flava, T. axillaris rubra, T. axillaris nigra*. According to my researches, *T. flava* is caused by a fungus of the genus *nocardia*, which I called *N. tenuis*. The red variety is caused by the same fungus plus a red-pigment-producing coccus, which I isolated and cultivated in various media, and which Chalmers and O'Connell called *Micrococcus Castellanii*. The black variety, *T. nigra*, is caused by the same nocardia (*N. tenuis*) plus a black-pigment-producing coccus, which I isolated and called *N. nigrescens*.

It is interesting to note that natives, especially African natives, seem to regard *T. axillaris* with disgust, and readily seek treatment, and Chalmers and O'Connell brought forward the hypothesis that the general custom of shaving the armpits among certain native tribes may have originated in their profound dislike of this complaint.

As regards treatment, I found in Ceylon that 1% formalin lotion applied to the armpits several times a day, and sulphur ointment at night, answered well.

Cryptococcosis Epidermica

Some years ago, while in Ceylon, I noticed on the skin of the arms of one of my bungalow servants several brownish patches which looked very much like dirt. He told me, however, that soap would not remove them. I made a

scraping, and I saw that these patches consisted of a large number of yeast-like organisms, which I did not succeed in cultivating. Later I found the same patches on many other natives and also on Europeans. *Cryptococcosis epidermica* must be differentiated from *Tinea flava* and *Tinea nigra*. In *Tinea flava* the color of the patches is bright yellow and the fungus has the characters of a *malassezia* and not of a *cryptococcus*. In *Tinea nigra* the patches are jet-black, the fungus is a chladosporium (*Chladosporium Mansoni Castellani*) and is easily cultivated. As regards treatment, salicylic acid in alcoholic solution or in an ointment, answers fairly well.

Dermatitis Interdigitalis Pedum (MANGO TOE)

A few remarks on this affection may not be out of place as, in my experience, it is often wrongly diagnosed, and if not properly treated becomes chronic and gives extreme discomfort. The condition is exceedingly common all over the Tropics, but is met with fairly frequently, especially in summer, also in Europe and America. The usual symptomatology is as follows:

The patient first complains of very severe itching, no lesions of any kind being visible; to relieve the terrible itching he scratches very hard, portions of the epidermis become removed, and small, superficial, red, irritable abrasions are seen. Later, in many cases, very painful fissures appear between the toes (*Dermatitis interdigitalis rimosa*). The *dermatitis* in the Tropics subsides spontaneously when the patient goes to the hills, but reappears as soon as he comes back to the lowlands. In Europe it often subsides spontaneously in the autumn and winter, to reappear in the late spring and summer, and this may go on for years. The symptoms are generally rendered much worse by wearing impermeable or badly ventilated boots.

The condition is due, as shown by Sabouraud and Whitfield, to localization, between the toes, of *Epidermophyton cruris* (*Castellani*), one of the fungi causing Dhobie's itch. Apparently the fungus may remain there quiescent, or seemingly quiescent, for a very long time, giving rise to practically no symptoms except pruritus and occasionally a little desquamation. The clinical appearance of the

condition does not, as a rule, suggest an epidermophytic or trychophytic origin, a papuloid eruption in circular, semicircular or festooned arrangement being quite exceptional. In a later stage, owing to the scratching, a secondary pyogenic infection—generally streptococcal—is often engrafted on the mycotic condition and vesicles may appear. Not rarely the mycotic-streptococcal infection of the toes extends to the soles of the feet, and numerous blebs and desquamating patches develop in that situation and are very difficult to cure (so-called "foot-tetter" or Hong-Kong foot of Cantlie). Occasionally the mycotic infection starts in the soles of the feet, and remains limited to that region without attacking the toes.

Treatment. A good routine treatment which Chalmers and I often used in Ceylon is the application, once or twice daily, of a 2% potassium permanganate lotion followed by a boric-acid talc powder—(*Ac. borici* finely powdered ʒi, *Talci* ʒi) or a dermatol talc powder (*Dermatol* ʒi, *Talci* ʒi). In certain cases a salicylic sulphur ointment or Tr. Iodine may be used, but not when deep, painful, cracks are present. In cases in which the inflammatory symptoms are acute, with eczematoid and pyogenic lesions, a soothing treatment is at first indicated, such as lead and opium lotion (*Lig. Plumbifort* ʒiiss, *Tr. Opii* ʒi. *Aqua dist. ad.* ʒvi) or a resorcin boric-acid lotion. (*Resorcin* gr xx, *aqua dist. ad.* ʒiv.)

The deep cracks may be touched, with care, with a solution of silver nitrate (2%). As soon as the severe inflammatory symptoms have subsided, the potassium-permanganate lotion may be used, or a sulphur salicylic-acid ointment (sulphur powder gr xv, *Ac. Salicyl.* gr. xv, *Vaseline ad* ʒi). Deeks' ointment is also very efficacious.

The patient should be directed to wear white stockings, changing them daily, and to sprinkle them with boric powder as well as the boots, which should not be air-tight. Canvas shoes are found by such patients to be a great comfort.

Tinea Flava

This condition is characterized by the presence of bright yellow, roundish or oval, patches on the skin of the face, neck, chest, abdomen and arms. A very large number of the natives of the low country of Ceylon and of many other

tropical countries, are affected. Sometimes the patches coalesce, giving rise to the diffuse form of the disease. Occasionally in Ceylon and Southern India one is surprised to see a Singalese or Tamil native with the face, chest and trunk of much lighter color than those of the other natives. On closer examination it will often be found that the apparently light color of the skin is merely due to a diffuse form of a very light variety of *Tinea flava*. Scrapings from the patches reveal presence of a fungus with the characteristics of a Malassezia, and morphologically very similar to the fungus found in *Pityriasis versicolor* of temperate zones. In fact, until recently *Tinea flava* was considered to be identical to *T. versicolor*.

I separated it from *T. versicolor* for the following reasons:

1. *Tinea flava* is of much lighter color.
2. It affects the face more frequently than any other part of the body, while *T. versicolor* is practically never found in that situation.
3. It is extremely chronic, developing in early childhood and lasting for life.
4. It is difficult to cure, while *T. versicolor* responds to treatment very readily.

The treatment of *Tinea flava* as I have already stated, is difficult; a sulphur salicylic ointment and turpentine are useful, and on covered parts of the body a crysophanic ointment (2%), or Tincture, or Liniment Iodine, may be used.

Tinea Nigra

This *dermatomycosis* is characterized by the presence of jet-black patches due to a fungus of the genus *Chladosporium*, which I called *C. mansoni* in honor of Sir Patrick Manson. This fungus is fairly easily grown on sugar media, giving rise to black colonies. The condition is fairly common in natives, but may be found also in Europeans as shown by the following case:—A European medical man went to Burmah from Ceylon for a pleasure trip. On coming back to Ceylon he noticed a roundish, very slightly elevated black spot on the palm of his left hand. This spot slowly increased in size for two months, becoming the size of a halfpenny-piece. A single application of formalin made it

disappear, but three months later it reappeared. A second application of formalin cured the condition permanently. From the patch, before treatment, cultures were made and a *chladosporium* was isolated identical to the fungus found in native cases.

Tinea Imbricata

This *dermatomycosis* which is so common in the Far East and certain islands of the Pacific, seems to be absent from Tropical America. The disease is of great interest clinically and ætiologically. Clinically, the term *tinea* applied to it is hardly correct, as the condition is totally different from the usual *trichophytoses* and *epidermophytoses*.

The development of the eruption is very interesting. A small, initial, brownish spot appears, generally on the arm, chest or back. After a few days this spot splits in the center, and in this way a ring of large, flaky scales is formed, with their bases towards the periphery; this scaly ring expands peripherally, and, while it does so, another brownish spot appears in the centre, at the same site as the first brown spot; this new brown patch also breaks in the centre, and in this way a second scaly ring is formed, which expands towards the periphery inside the first ring; again, in the centre a dark patch appears, which splits, and a third ring is formed inside the second; and so on, until a number of scaly rings are developed.

Manson aptly compared this development of concentric rings to the concentric ripples produced by a pebble thrown into a pool of water.

The scales are flaky, tissue-paper-like, of large size, up to ½-inch in length, dry, and of a dirty greyish or brownish colour. In my experience, the fungus never invades the hair follicles, but it often invades the nails.

The disease has no tendency to spontaneous cure. As regards the ætiology of the disease, it is stated in most books that it is an *aspergillomycosis*. After an investigation extending over several years, I came to the conclusion that *aspergilli* have nothing to do with the ætiology of the malady. True, they are often found in the scales and are grown, but they are saprophytic. The inoculation of cultures of these fungi in human beings does not reproduce the disease. The

TINEA IMBRICATA

true causative agents of the condition are peculiar fungi, for the isolation of which a special method of cultivation has to be used.

I have suggested the creation of a new genus for these fungi: *Endodermophyton*. Morphologically and culturally they are closely allied to the *Achorions*. I have isolated 3 principal species: *E. tropicales*, *E. Indicum*, and *E. Concentricum*. (The botanical description of these fungi may be found in the chapter on Tinea Imbricata in Castellani and Chalmer's Manual of Tropical Medicine, 3d Edition.)

PROGNOSIS AND TREATMENT

The disease has no tendency whatever to spontaneous cure, and its treatment is very difficult. In the Colombo Clinique of Tropical Medicine I tried a large number of different ointments, lotions, etc., and came to the conclusion that the best routine treatment is by resorcin (1-2 dr.) dissolved in tincture benzoin compound (1 oz.) or by chrysarobin ointment. It is interesting to note that resorcin, in ointment or in alcoholic solution, has practically no action, and that tincture-benzoin compound, alone, has also practically no action, but that when the resorcin is dissolved in the tincture very good results are obtained.

A NEW TYPE OF *Blastomycosis cutis* (*Furunculosis cryptococcica decalvans*)

The usual type of *blastomycosis cutis* is well known, thanks principally to the work of American observers; it is clinically characterized by the presence of patches with papillary excrescences, which give them a characteristic warty, or verrucose, or cauliflower appearance. The face, hands and arms are the areas most frequently attacked.

I should like to call attention to a type of *blastomycosis* (*sensu lato*) which has clinically a totally different aspect, a condition that clinically can hardly be distinguished from ordinary severe *furunculosis*. I have called it *Furunculosis cryptococcica*. It attacks the scalp principally, causing loss of hair (*Folliculitis decalvans cryptoccocica*). The eruption in most cases apparently begins as a follicular *pyosis* of the scalp, each pustule of which may be flattened or conical, being pierced by a hair; in addition there may be infiltrated lesions, somewhat resembling flat carbuncles, which later on open and discharge through several openings. The hair in the affected areas falls off, and patches of baldness sometimes permanently remain. As regards the lesions on the face and body, these are practically indistinguishable from severe boils. It is interesting to note that in certain cases the lesions on the body are very few or absent altogether, and the condition is practically limited to the scalp: in these cases the term *Folliculitis decalvans cryptococcica* is more appropriate.

FOLLICULITIS DECALVANS CRYPTOCOCCICA

Illustrative case.—Mr. D., married, 34 years of age, a Dane residing in London for the last 12 years, very keen on all outdoor sports, and a famous "footballer." The condition started in March, 1921, with apparently follicular pustules on the scalp and 2 or 3 furunculus-like lesions on the forehead and face. Later, extremely painful carbuncle-like lesions developed. His medical attendant had a bacteriological examination of the pus made at a well-known

clinical laboratory in London, and *Staphylococcus aureus* was found. An autogeneous *staphylococcus* vaccine, and also stock vaccine, were given for 18 months without any benefit. On the advice of his medical attendant the patient then came to consult me.

Apart from a boil on the left forearm, and one on the supra-orbital region, all the lesions were on the scalp; several patches of baldness, with the skin smooth and whitish, were plainly visible; there were also a number of follicular pustules, some flat, some conical, most of them surrounded by a zone of hyperæmia; 2 extremely painful carbuncle-like lesions, one not yet opened, the other with several openings discharging. I made a bacteriological and mycological examination. Microscopically the pus contained only gram-positive cocci. The glucose agar tubes inoculated with the pus showed abundant growth of *Staphylococcus aureus*. The microscopical examination of the growth, however, showed here and there a yeast-like cell in several tubes. After plating and replating, this yeast-like organism was isolated with great difficulty. Later I grew the same fungus from a number of lesions.

The fungus is a *cryptococcus* with the following principal characters: cultures on glucose agar abundant with smooth surface, at first white, later yellowish. The fungus does not produce gas in any carbohydrate. It was agglutinated by the patient's blood in high dilution (1 in 400). An interesting point arises: Which organism was the true causative agent of the condition—the *cryptococcus* or the *staphylococcus*? In my opinion it was the *cryptococcus*, for the following reasons:

(1) *Staphylococcus* vaccines had no beneficial action whatever.

(2) The *cryptococcus* was agglutinated by the patient's blood, and the condition improved, and finally got well, on a treatment consisting of giving massive doses of potassium iodide internally, and a *cryptococcus* vaccine by subcutaneous injection. It is well known that potassium iodide not only has no beneficial action in *staphylococcus furunculosis*, but it makes it much worse.

Pruritus ani OF MYCOTIC ORIGIN

An enormous number of different drugs have been recommended in *pruritus ani;* a given drug will answer well in certain cases, and will have no action whatever in others. This shows that *pruritus ani* must be of very different ætiological origin. As a matter of fact, this has been recognized for many years, and several types of *pruritus ani* have been differentiated, including a *bacterial* type, certain authorities believing the condition to be of *streptococcus* origin.

I should like to call attention to a variety of *Pruritus ani* which, in all probability, is of *mycotic* origin. During the last 12 years I have had the opportunity of examining and investigating 52 cases of so-called *pruritus ani*, and in 9 cases I have grown from scrapings of the ano-perianal region, using mycological methods of cultivation, fungi of the genera *Epidermophyton* and *Trichophyton*, viz., *Ep. cruris Castellani* (1905)=*Ep. inguinale Sabauraud*, (1907) in 6 cases; *E. rubrum Castellani* (1909) in 2 cases; a *trichophyton* not yet classified, in 1 case. Apparently fungi of the genus *Epidermophyton* may remain dormant in the perianal region for a long time, causing severe *pruritus*, but practically no objective symptoms, though if the region is examined carefully small, red, infiltrated patches may not rarely be seen. An eczematous *dermatitis* due to scratching may also develop, and a secondary *streptococcus* infection may become engrafted on the mycotic condition. This mycotic type of *pruritus ani* may be compared with the well-known *pruritus interdigitalis pedum* in which there is practically no objective sign of an *epidermophyton* infection.

None of my 9 cases presented active symptoms of Dhobie's itch (*Tinea cruris*) of the inguinal region, but 6 gave a history of having suffered from it years previously; 2 of the cases were suffering also from *pruritus interdigitalis pedum*, and in both cases *Epidermophyton cruris* was isolated from the scrapings of the skin of the toes.

In my experience *pruritus ani* of *mycotic* origin has no tendency to spontaneous cure. The fungus remains in the perianal region indefinitely, practically dormant, but giving rise to severe *pruritus*, which, however, may stop completely for certain periods of time.

Treatment.—I have found that silver nitrate is often very efficacious (*arg. nitr.* gr. xv, *Spir. æther. nitr.* ℥i), but it should be applied with great care. An ointment containing 2 grains of *crysobarin* to the ounce of vaseline is sometimes effective. This, too, should be used with great care. Painting the parts with a strong lotion of potassium permanganate (gr. xxx to water ℥i) is useful in certain cases—also an ointment containing salicylic acid and sulphur (gr. x of each to 1 oz. of vaseline). When an eczematous *dermatitis* due to scratching is present with severe acute symptoms of inflammation, a soothing treatment should at first be used, such as lead lotion. When the acute symptoms have disappeared, the *anti-mycotic* treatment should be started. It is interesting to note that Deeks' ointment has been found very efficacious by Deeks and others in a number of cases of *pruritus ani;* this, I think, supports my belief that a certain number of cases of *pruritus ani* are of mycotic origin, because the ointment is powerfully *anti-mycotic,* containing salicylic acid, mercury salicylate and eucalyptus oil.

LITTLE-KNOWN PIGMENTARY CONDITIONS

Dermatosis festonala frontalis.—This affection, which is not frequent, is found in Europeans who have resided for many years in the Tropics, who have lived an open-air life, such as that of planters and overseers, and who have exposed themselves to the sun for long periods of time. In a well-marked case the *dermatosis* has a festooned appearance, the margin being at times slightly raised, often of a vivid bright red or coppery-red color, while the skin which it encircles has a peculiar whitish, occasionally leucoderma-like, appearance and may be slightly atrophied; at times small patches of hyperpigmentation are scattered about. There is very little or no *pruritus,* and sensation of pain, heat, etc., is normal. The course is extremely long, the lesions slowly expanding peripherally.

This affection is often diagnosed as a *trycophytic* condition, owing to the festooned edge, but the microscopical and cultural examination of scrapings from the edge, etc., never reveals any fungus. In the Tropics it is not rarely mistaken for leprosy, from which it can easily be distin-

guished by the sensations being normal. It is not a syphilide, as salvarsan, mercury and potassium iodide have no action on it. Probably continuous exposure to the sun and glare play an important role in its ætiology.

Prognosis and treatment. The condition has no tendency to spontaneous cure, in the Tropics; but it gets much better and may ultimately disappear completely if the patient goes to reside in a cold country. The treatment is very unsatisfactory. The patient must be advised not to expose himself to the sun and glare, and he should wear a wide-brimmed tope, or sun-helmet, lined with red or green cloth. The only drug which occasionally seems to do some good is ichthyol: a 5-grain tablet 3 times daily before meals. An ichthyol lotion or ointment (5%) should be applied to the affected skin at night; during the day calamine lotion may be used.

Melanonychia

The condition is characterized by a band of black pigmentation along the free border of the nail. On superficial examination, it has the same appearance as though some dirt had accumulated beneath the free border of the nail but, on scraping, this pigmentation does not disappear. In all the cases I have seen the general condition was good; none of the patients were using any internal medicine or external toilet preparation which could account for the pigmentation in any way. The pigmentation generally disappears spontaneously within from 6 months to a year.

The Yellow Disease (*Ochrodermatosis*).—This very peculiar pigmentary condition of obscure origin was first described by me some years ago in Ceylon, but I have seen cases in other tropical countries. The hands, arms, face and at times the whole body are of a bright yellow or canary yellow quite different from the yellowish-green color of jaundice. The *sclerotic*æ remain completely white; the urine is of normal color and composition; the stools are not decolorized; the liver and spleen are not enlarged; and the general state of health is quite good. The condition is easily distinguished from *ochronosis* and from *Xanthoderma arcatum*. Ochronosis is generally congenital, there is *alcaptomoria*, and the ligaments and cartilages become blackened. In *Xanthoderma*

arcatum the yellow patches remain localized in the legs, and are permanent.

Treatment.—No internal or external treatment is, in my experience, of any use. The condition, however, greatly improves or disappears completely on the patient's leaving the low country and going to some hill station, or better still to Europe or North America.

DISCUSSION

Dr. Roland C. Connor (Opening the Discussion). — I want to congratulate Dr. Castellani for the most interesting demonstration and talk on skin diseases to which it has ever been my pleasure to listen. This subject has interested me very much because we on the Isthmus have never been favored by having any research work whatever done on tropical skin-diseases, or on plant *dermatitis* due to different plants in our tropical regions; and I must say that practically all the information and help I have been able to get has been secured from literature contributed by him and other workers in the Far East. They have furnished the basis for all my work in the diagnosis and treatment of most of our tropical skin-diseases. Dr. Castellani has shown me many of my old friends in his numerous lantern illustrations tonight.

There is a practical point in the prevention of *tinea cruris* and some of the common forms of Dhobie's itch, that I discovered by chance on my own self in 1907. We were using salicylic acid and alcohol and, later on, Dr. Deeks' Dhobie's-itch ointment, a mercury, salicylic acid, and oil of eucalyptus mixture. I found that the *tinea cruris* affection frequently relapsed after an apparent cure. It occurred to me that an excessive acid perspiration was conducive to the growth of this fungus, so I began the use of an alkaline powder, after bath, when I had apparently cured the infection. I put a tablespoonful of bicarbonate of soda in about 8 ounces of perfumed talcum powder, mixed thoroughly, and used it. I never have had a recurrence of *tinea cruris*, and I always recommend the use of the preparation to my patients after they have been treated and cured of the affection. The same applies to common *tinea* infections between the toes and on the feet, where the affection is often rebellious to treatment.

Many years ago I took a hint from Dr. Deeks — who prescribed his Dhobie's-itch ointment in a case of *pruritus ani* — with great relief to the patient, and I have many times had the opportunity of noting the relief that this remedy gave in many cases of *pruritus ani*, in which none of the common causes of the trouble could be

found. Only a small bit need be used, and should be applied once or twice a day on the tip of the finger and rubbed in well about the anal orifice. No doubt, the relief experienced in these cases was due to the parasiticidal effect of the remedy on the fungus described by Dr. Castellani as causing *pruritus ani* in cases noted by him.

Dr. Castellani (*Closing the discussion of his own paper*). — I was very much interested in what Dr. Connor said about the relapses of Dhobie's itch. This has been the experience of all of us, and I certainly think that his powder should be generally used. As regards *pruritus ani*, I am very much interested to hear that the Dhobie's-itch ointment suggested by that fine clinician, Dr. Deeks, gives very good results in many cases of this condition, because that is really in favor of my theory that a certain percentage of such cases are of *mycotic* origin.

MYCOSIS OF THE HANDS AND FEET

C. S. Butler, M.D., J. E. Houghton, M.D.,
and G. F. Cooper, M.D.

(Read by Title)

The title of this paper, "Mycosis of the Hands and Feet," indicates our belief that several moulds are implicated and not Epidermophyton alone. There were 12 genera involved in Greenwood's study in Boston[1]. Sequeira, in his work on Diseases of the Skin, recognizes three species as being rather common in these lesions. They are *Epidermophyton cruris*, (Cart.), *E. perneti*, (Cart.), and *E. rubrum* (Cart.) (*Trichophyton purpureum*) (Baug). These produce the condition which is known as "Dhobie itch."

Kaufmann-Wolf[2], quotes Sabouraud as having found, in addition to *Epidermophyton cruris*, also *Microsporon lanosum*, *Achorion quinckeanum*, and *Trichophyton gypseum* in these lesions. This author implies that *E. cruris* is common in the lesions as found in Berlin, Vienna and Paris. White and Greenwood[3] make the statement that species of *Epidermophyton* and *Trichophyton* are usually found in Boston. In the observations made at the Naval Medical School, the fungi causing this dermatomycosis were found to belong to three genera: *Microsporon*, *Trichophyton*, and *Epidermophyton*. The term *epidermophytosis* is therefore not, strictly speaking, correct, as the name would imply that all forms of this disease are due to epidermophytons. We think it may be put down as correct that by long odds the organisms chiefly involved in the production of lesions of the types under consideration, are the same as those responsible for the so-called Dhobie itch, crutch itch, intertrigo of the axillary space, and elsewhere. *Epidermophyton*, as distinguished from *Trichophyton*, does not grow on the hair

[1] Greenwood, A. M., "Report on Cultures of Parasitic Fungi"; *Arch. Dermat. and Syph.*, 8, pp. 81–82, 1923.

[2] Kaufmann-Wolf, M., "Fungus Diseases of the Hands and Feet"; *Dermatologishche Zeitschrift*, 1914.

[3] White, C. G., and Greenwood, A. M., "Epidermophytosis;" *Journ. Am. Med. Assn.*, 77:1297 (Oct.) 1921.

nor in the shaft of the hair. These are the 2 genera chiefly involved.

The rôle played by the higher fungi in human pathology at the present time is given very little thought. Attention is devoted to the bacteria. Medical mycology[1] came into existence long before bacteriology. It may be said to have begun in 1839 when Langenbeck discovered the fungus of thrush, which was later named *Oidium albicans* by Charles Robin. Following Langenbeck's discovery, the fungus of ringworm was found by Gruby and Malassez in 1844. The discoveries of Pasteur and Koch brought bacteriology to the forefront and medical mycology was unfortunately overlooked. Castellani estimates that twenty percent. more tropical infections are caused by fungi higher than bacteria. Medical mycology has not advanced very far. The classifications and methods of identification are hazy and the differences among the various genera are slight.

The types of lesions recognized by most dermatologists as produced by these organisms are: (*a*) The acute vesicular or bullous; (*b*) The intertriginous, and (*c*) The hyperkeratotic. Some others recognize a (*d*) squamous type. (*e*) A lardaceous type is also recognized by some authorities. These names are sufficiently descriptive and one of the pictures will show examples of each of the several types. (See Plate II.)

Geographical Distribution

The geographical distribution of Eczematoid dermatitis of the hands and feet may be said to be world-wide. The experience of dermatologists in the United States shows its extreme prevalence in such widely separated places as New Orleans, San Francisco, Chicago, Washington and Boston. As for Europe, the works of Kaufmann-Wolf, Sabouraud, Tilbury Fox, Hebra and others show this complaint to be prevalent in England, France, Germany, Austria, and elsewhere. The studies of Castellani, and those of medical officers of the armies and navies of different governments, show the extreme prevalence of the complaint throughout all the tropical belt. It is probable that the World War served

[1] Castellani, A., "Medical Mycology." *Journ. Trop. Med. and Hyg.* XXVII, p. 49, March *1*, 1924.

to supply to every nation participating such mycotic strains as they may not have formerly possessed.

EPIDEMIOLOGY

The name "Dhobie itch" seems to attach etiological importance to the washerman, for that is what the name dhobie means. The idea has been prevalent that the spores of these organisms are transferred in the process of laundering, from infected clothes to those which are not infected. In view of the extreme prevalence of this complaint in every country, and in view of the much more plausible method of transfer than by clean clothing, it is thought that the stigma which attaches to the washerman as a purveyor of epidermophytosis should be removed. There are no figures, so far as we know, showing the relative incidence of epidermophytosis in men and in women.

Our observations have been made almost entirely upon men, but from talking with many dermatologists it is our belief that the condition is far more prevalent among men than among women; 4 to 1 in the Boston figures. This fact has its lesson in the matter of prophylaxis. Lesions are frequently seen on other parts of the body than the hands and feet, so that there is great chance of infection being conveyed by means of common wash basins, common towels, the ordinary bathtub, and the seat of the toilet. It is potentially venereal. It requires no stretch of the imagination to conceive of the infection being transferred by shaking hands. When one considers the prevalence of lesions on the hands, it is remarkable that more people do not suffer from it than actually seems to be the case. Epidermophytosis should discourage promiscuous handshaking. This disease often spreads in families and institutions and is very difficult to eradicate when it thus gains a foothold. It is of great importance to soldiers and sailors, not only on account of the intimate contacts which are made in barracks and on board ship, enhancing the chance of transfer, but in many cases by reason of superadded infections (pus infections) of the soles of the feet, it is a very real menace to landing expeditions and to infantry soldiers in general.

Except through these superadded infections there is very little danger to life, but when we consider the chronicity of

the infection and the fact that it may carry over in the intact skin from season to season, may last for a lifetime in this way and upon occasion give rise to much irritation of the areas affected, its importance deserves widespread recognition. Gradually since about 1869 the importance of epidermophytosis has come to be recognized. Dermatologists at the present time are well aware of the damage it may cause and its great annoyance to those infected, but the general practitioner goes along and treats lesions of this character as if they were eczema, pompholyx, etc., with the result that the disease is not cured because it is never recognized for what it really is.

For the purpose of determining the incidence of hand and foot mycosis in the U. S. Naval Service, a survey of 500 individuals was made and the results were tabulated as shown in the accompanying charts.

A questionnaire was devised and completed, not by the individual himself filling in the spaces, but by personally interviewing each person in regard to past history of ringworm infections, special stress being placed on present and previous crural infection. The following questions were asked: (1) Name, rate, corps; (2) Place of birth; (3) Tropical service; (4) How long? (5) Where? (6) Ringworm infections on the body; (7) Location; (8) Duration; (9) Treatment, if any, and by whom? (10) Lesions at present; (11) Ringworm on hands and feet; (12) Location; (13) Duration; (14) Treatment, if any, and by whom? (15) Lesions at present.

If no history of hand or foot infection was claimed, each person was questioned as to previous "Dhobie itch" and "Spick itch" infection. The vesicular and scaly lesions occurring on the hands and feet were described, as many of the men interviewed were not clear as to the meaning of the term "ringworm," when applied to lesions of the hands and feet. If a history of existing mycosis was elicited, the lesions were examined and, if they resembled any of the different types recognized, the man was asked to come to the laboratory for further study.

The survey was made among 4 groups of men; officers, marines, patients in the Naval Hospital and enlisted men of the Hospital Corps. As several of the patients in the Hospital were marines, and a few were Veterans' Bureau patients,

Chart II shows them grouped in this manner.

In view of the chronicity of the lesions in a true mycosis, attention was given to duration in cases of doubtful history before they were classified as positive. If the individual stated that the condition had lasted only a few days and he was cured by some simple remedy, his lesions were not considered to be of fungous origin. On the other hand, if they

INCIDENCE OF RINGWORM

	Marines	Patients in Hospital	Officers	Hospital Corpsmen	Total
	293	176	11	20	500
Tropical Duty.....	69	79	9	9	166
Percent.....	23.5%	44.8%	81.8%	45%	33.2%
Ringworm other than Hands and Feet...	65	31	2	6	104
Percent.....	22.2%	17.6%	18.1%	30%	20.8%
Ringworm on Hands and Feet.....	8	47	10	11	76
Percent.....	2.7%	26.7%	90.9%	55%	13.2%
Average Duration of Lesions.....	1.4 yrs.	1.68 yrs.	1.6 yrs.	1.1 yrs.	1.42 yrs.
Active Lesions at Present.....	5	6	3	2	16
Percent.....	1.7%	3.4%	27.2%	10%	3.2%
Mould Demonstrated	5	3	2	1	11
Percent.....	100%	50%	66.6%	50%	68.7%

TYPES OF LESION SEEN

Vesicular, Number..	5	3	3	2	13
Squamous, Number.	1	0	0	0	1
Hyperkeratotic Number.....	1	1	0	0	2
Intertriginous Number.....	1	2	0	0	3

CHART NO. I

RELATION OF TROPICAL DUTY TO RINGWORM INFECTION OF HANDS AND FEET AND OTHER PARTS OF BODY

	Service	Marines	Sailors	Officers	Vet. Bur	Total
		355	91	11	43	500
Ringworm of Hands and Feet.....	Tropical	15	21	9	4	49
	None	10	10	1	6	27
Ringworm of Body—other than Hands and Feet.....	Tropical	34	16	2	1	53
	None	42	6	0	3	51

CHART NO. II

followed a crural or other ringworm infection, much more weight was given to their probable mycotic nature.

When the man reported to the laboratory, ringworm fungi were searched for microscopically, as follows: The vesicles, if present, were cleansed with alcohol and pierced at their base with a narrow, sharp scalpel, the point passing through the vesicle and cutting out one side. This free edge was then grasped with a thumb forceps and the remaining attachment severed with the knife. The roof of the vesicle, thus obtained, was inverted on a clean slide, covered by a drop of 15% sodium hydrate solution, and the specimen covered and pressed out with a vaseline-ringed coverglass.

Usually the mould could be demonstrated, when present, within from 5 to 30 minutes, according to the thickness of the vesicle. The more keratotic the lesion, the longer the time required by the NaOH for clearing, and vice versa. The fungi were demonstrated in practically every case in which the vesicle was typical and unbroken. If the fungi were demonstrated, the case was studied by cultural methods to determine the type of mould, as described under the section on mycology.

Information obtained by use of the questionnaires was assembled, and averages and percentages were studied to determine what rôle is played in this type of mycosis by tropical service, the geographical incidence as shown by birthplace, relation to ringworm on other parts of the body, and the duration of the lesions in the average case.

TROPICAL SERVICE

In 3 of the 4 groups shown on Chart II, the majority of those having ringworm infections of the hands and feet, have had tropical duty. In all 4 groups 49 cases had had tropical duty while 27 had not. Of those having had ringworm on the body other than on the hands and feet, 53 had had tropical duty and 51 had not, *i.e.*, practically an even number of each.

RINGWORM INFECTIONS OF THE HANDS AND FEET

As shown in Chart I, the following percentages are found in the 4 groups: Marines 2.7%; patients in Hospital (marines, sailors and Veterans' Bureau patients) 26.7%; officers 90.0%, and hospital corpsmen 55%, with an average for all 4 groups of 13.2%. The enlisted men of the Hospital Corps and the officers being the smallest group, and also showing the highest percentage of infection, there is speculation as to whether or not this is to some extent due to constant handling of patients, or, in the case of officers, to their permanent status, while the other groups are constantly changing by enlistment and discharge.

RINGWORM OF THE BODY OTHER THAN ON THE HANDS AND FEET

As the figures in Chart II indicate that there is about an even number of individuals in this group irrespective of tropical duty, it likewise shows a fairly constant figure of incidence among the 4 groups, *viz.*, marines 22.2%; patients in hospitals 17.6%; officers 18.1%; and hospital corpsmen 30%, with an average for all groups of 20.8%.

AVERAGE DURATION OF LESIONS

The figures under this heading are the most constant of all, the variations being very slight in all groups, although the men gave histories of duration, in individual cases, ranging from 6 months to 24 years. The average of the total number was 1.42 years.

ACTIVE LESIONS AT PRESENT

Sixteen cases having active lesions were found among the 500 persons included in the survey, or 3.2%.

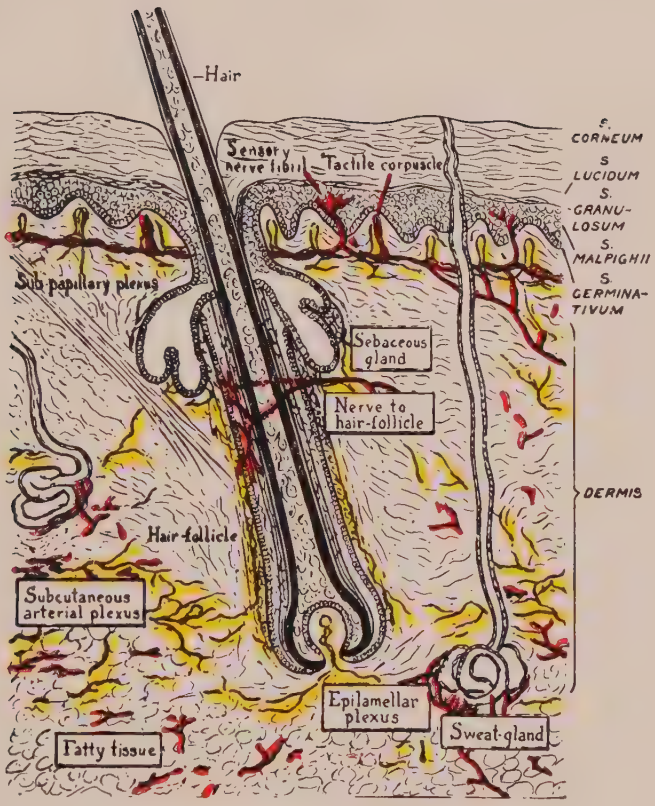


PLATE I. HISTOLOGY OF THE SKIN

Black — Outlines of glands, follicle and general cell structure
Yellow — Arterioles and capillaries
Red — Nerves, nerve fibrils and tactile corpuscles

SHOWING RELATIVE PERCENTAGE AMONG DIFFERENT GROUPS, CLASSIFIED AS TO LOCATION OF RINGWORM AND SERVICE.

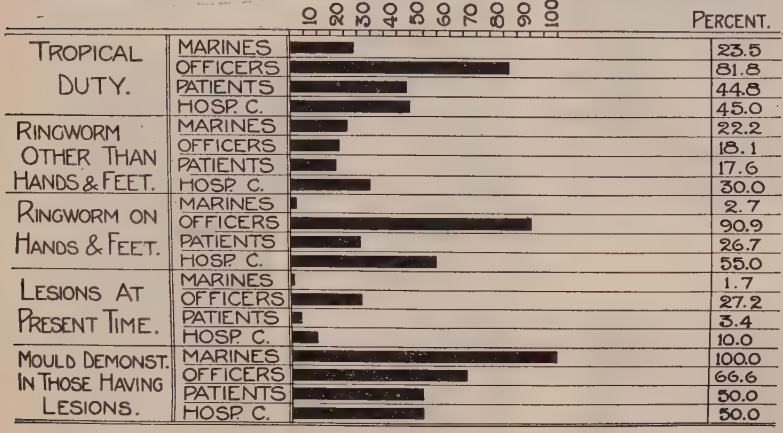


CHART NO. III.

DEMONSTRATION OF FUNGI IN THE LESIONS

Of the 16 cases found, the mould was demonstrated in the vesicles or scales in 11 cases, the highest percentage being among the marines, of whom 5 had vesicles present, and the fungus was found microscopically in the dome of the vesicle in all 5 cases. Of the total of 16 cases, the percentage of positives by microscopical examination was 68.

TYPES OF LESION SEEN

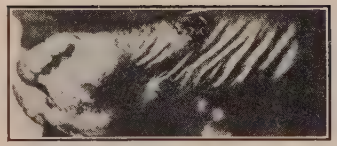
Among the 16 cases described above, all the types described elsewhere in this paper were noted, some cases presenting 2 or more types. As shown by Chart I, the following numbers of the 4 types were seen: Acute vesicular 13; squamous 1; hyperkeratotic 2; and intertriginous 3.

PATHOLOGY

Plate I shows the histology of the skin and the relation of the blood vessels, nerves, sebaceous and sweat glands, hair follicles, etc. Plate II, which is a composite made from the illustrations of Kaufmann-Wolf[1], will show sections of skin through a series of vesicles and also several types of lesion.

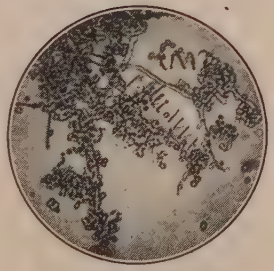
[1] KAUFMANN-WOLF, M., "Fungus Diseases of the Hands and Feet"; *Dermatologishche Zeitschrift*, 1914.

Dysidrosislike mycosis of the feet (Ephidermophyton inguinale) in the stage of scaling following a severe inflammation.

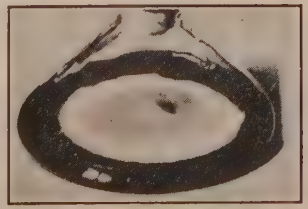


Early mould lesion on the external border of the foot. The younger lesions on the plantar surface show the scaling border plainly.

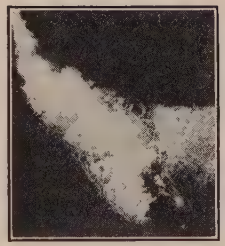
Spreading mould focus, considerable pus formation.



Photomicrograph Culture particle in potash solution.

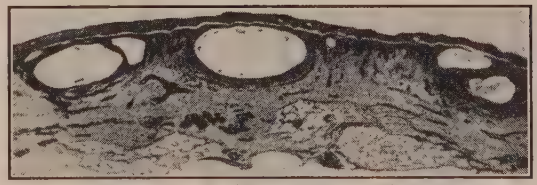


Concentric arrangement of culture spoken of in text.

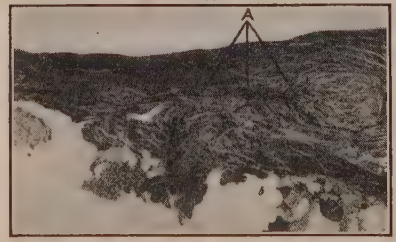


Serpiginous, scaly mycotic lesion extending upon the dorsum.

Scaling mould lesion of the palmar surface.



Appearance of a section through a group of vesicles on the plantar surface (general appearance).



View of the horny layer of the plantar surface (whole vesicles)

(*a*) Mycelium.
(*b*) Vesicle contents.

PLATE NO. II

It will be noted that the mould grows entirely in the epidermis and apparently does not involve the derma at all. There are leucocytes in the vesicle contents and from this fact one would think that perhaps antibodies might be formed in response to *epidermophyton* infections. The vesicle, which may be considered as the primary lesion of this infection, has no connection with the sweat glands, and its contents are not sweat, though hyperhydrosis may result from the lesions, probably owing to congestion. According to Kaufmann-Wolfe[1] the contents consist of fibrin, leucocytes, nuclei, and poorly-defined fragments of cells. Fungus elements are not to be seen as such but the glycerin-like material which comes from puncture of one of these vesicles is infectious, and the mould is cultivable from it. The layer of epidermis overlying this vesicle is the best tissue in which to find the organisms. It is not often possible, in our experience, to find the organism in preparations made from hyperkeratotic and serpiginous lesions. In the sodden epidermis of soft corns it may be occasionally found, but the best lesion from which to make an exact diagnosis is the vesicle.

MYCOLOGY

A considerable amount of work has been done upon the culture of these moulds. Sabouraud not only has described the culture characteristics of species of *Epidermophyton*, but has studied and given the culture characters of many other parasitic moulds. Greenwood and White[2], Hopkins and Iwamoto[3], Castellani[4], Ormsby and Mitchell[5], and others have studied the culture characters and fermentative reactions of these strains of mould, so that the several species are pretty well defined as to changes which they produce in

[1] KAUFMANN-WOLF, M., "Fungus Diseases of the Hands and Feet"; *Dermatologishche Zeitschrift*, 1914.

[2] WHITE, C. G., and GREENWOOD, A. M., "Epidermophytosis"; *Journ. Am. Med. Assn.*, 77:1297 (Oct.) 1921.

[3] HOPKINS, J. G., and IWAMOTO, K., "Fermentation Reactions of the Ringworm Fungi": I. "Differentiation of the Trichophyta and Allied Genera from Other Fungi"; *Arch. Derm. & Syph.*, 8:619 (Nov.) 1923.

[4] CASTELLANI, A., "Medical Mycology," *Journ. Trop. Med. and Hyg.* XXVII, 5, p. 49, March 1, 1924.

[5] ORMSBY, O. S., and MITCHELL, J. H., "Ringworm of Hands and Feet"; *Journ. Am. Med. Assn.*, 67:10, p. 111 (Sept.) 1916.

sugar media and on different culture media. For the purpose of diagnosis and treatment it would seem to us a waste of time to try to culture them.

If the proper type of lesion is studied and the proper technique is carried out in clearing up the portion of the vesicle which is taken, it is practically always possible to demonstrate the causative organism. It often requires persever-

PLATE IIIA.

Photograph showing the chronic hyperkeratotic type of lesion. Marine case of 6 months' duration.

ance, however. Cultures of these moulds are very often contaminated with bacteria, even though the gross appearance of the culture would not disclose the fact. Efforts to separate them on the basis of carbohydrate fermentations are very worthy, but it would seem to us that it is a lot of

work with very little dependable information to be expected in the end, so that for diagnosis it seems that culture is useless.

The vegetative mycelial forms found in the tissues (scales and vesicles) (Plate III) are practically all alike, with very slight morphological differences, so that the recognition of species and genera lies in the manner of growth and reproduction by cultivation on artificial media. Cultural differentiations are, however, most difficult, owing to the pleomorphic forms which most of the fungi assume on artificial media containing sugar. The characteristics of the original cultures are often so altered by varying periods of growth on the various media that colony identification is impossible. The distinguishing features must lie in the use of a universally standard culture medium, and that devised by Sabouraud is known as the international proof medium, so that the results in different countries might agree. The difficulty has been in obtaining the materials recommended by Sabouraud, namely, the French peptone (Peptone Chassaing) and the French maltose (Chanut's maltose brute).

For fermentation reactions Hopkins and Iwamoto[1] found it practicable to use a synthetic inorganic medium devised by Currie for the study of citric acid production by *Aspergillus*. Various fermentable substances were added and an indicator to denote the production of acidity. On this medium (#) they found that fungi which grew well on any particular carbohydrate usually produced sufficient acid to change the indicator (Andrade) to red.

#Currie's medium:	Ammonium nitrate	2.5
	Diacid potassium phosphate	1.0
	Magnesium sulphate (crystal)	.25
	Water	1000.0

Add 1.5% agar, 1% of carbohydrate to be tested and 0.5% of Andrade's indicator.

This change appeared after a variable interval, which was somewhat dependent on the rapidity of the growth. Transitory or prolonged periods of acidity were found to be respec-

[1] HOPKINS, J. G., and IWAMOTO, K., "Fermentation Reactions of the Ringworm Fungi": I. "Differentiation of the Trichophyta and Allied Genera from Other Fungi"; *Arch. Derm. & Syph.*, 8:619 (Nov.) 1923.

tively fairly characteristic of certain strains. With the addition of peptone no reddening of the indicator was observed, although control tubes without peptone reacted positively. They assume that the acid production was masked by alkali production from peptone. Observations were made on 19 of Sabouraud's original dermatophytes and over 100 strains of ringworm fungi isolated in the United States.

Hopkins' experiments show that certain strains of the parasitic ringworm fungi utilize mannite, mannose, glucose and fructose by a process of acid fermentation, while none of these strains ferment lactose, saccharose, xylose or arabinose. The common skin saprophytes and air contaminants grow easily and produce acid reactions on carbohydrate-containing media, which are not utilizable by the ringworm fungi. By the use of these media on the basis of definite reactions they divide the ringworm fungi into 3 groups, Group A being the slow fermenting varieties; Group B the intermediates; Group C the rapidly fermenting varieties. Using a double sugar-tube containing lactose and saccharose and a tube of media containing mannite, it is possible to differentiate the parasitic from the saprophytic fungi and this is undoubtedly a most valuable supplement to morphological study in the identification of these fungi.

In order to avoid confusion of terms that do not mean the same thing to every reader, we wish to quote these of White and Greenwood,[1] which more clearly describe the morphological characteristics of the fungi, than they have been described elsewhere.

(1) Hypha: The vegetative part of a fungus; a fungus filament; long cylindric, branched filamentous cells which have a continued apical growth.

(2) Mycelium: A mass of hyphae.

(3) Spore: The primary reproductive body of the fungi; primarily a single cell separated from the lower plants for purposes of reproduction. Spores perform a function in the fungi analogous to that of seeds in the higher plants. The majority of fungi produce more than one kind of spore. In the genera *Trichophyton* and *Epidermophyton* three types are

[1] WHITE, C. G., and GREENWOOD, A. M., "Epidermophytosis"; *Journ. Am. Med. Assn.*, 77:1297 (Oct.) 1921.

produced: Conidia of the sporotrichum type (microconidia) macroconidia (fuseax, spindles) and chlamydospores.

(4) Conidium: A sexual spore arising from the hypha by budding or septation. They may develop terminally or laterally or both; at first unicellular, they may become pluricellular.

(5) Chlamydospore: A spore formed in the continuity of a hypha and encysted.

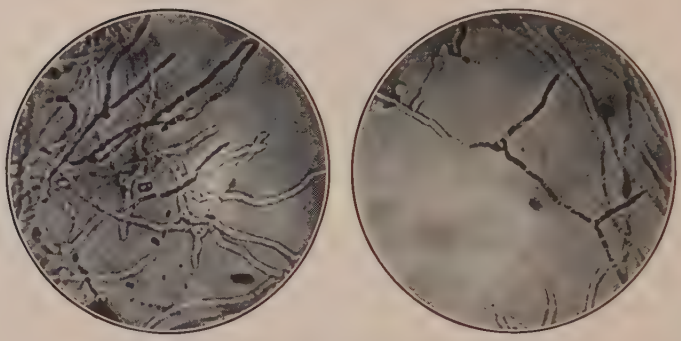
(6) Among the conidia in this group of fungi is a type called by the French "fuseaux" (spindles), which is a larger and a particularly differentiated type. It is more or less spindle-shaped, thick-walled and sometimes septate transversely in these genera. It is a macroconidium. The shape of these spindles is characteristic in *Epidermophyton* and *Microsporon*, but less so in *Trichophyton*.

(7) Ascus: A sac-like cell within which is formed a definite number of spores by a highly complicated process. Generally it contains 2, 4, 8 or a multiple-of-8 spores.

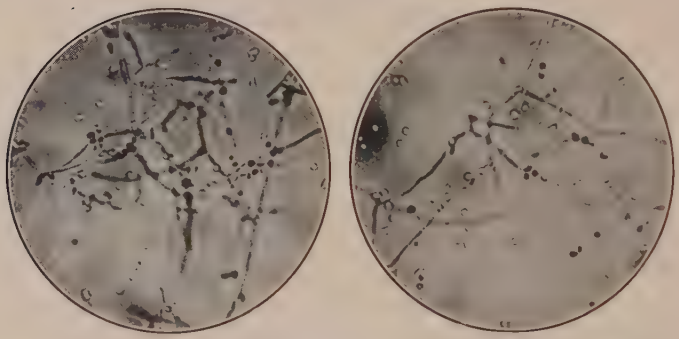
It is usually considered that these genera — *Trichophyton* and *Epidermophyton* — when parasitic on man show only the vegetative forms, *i.e.*, the production of hyphae and mycelium. The decision as to whether the "sporoid bodies" found in the scales and scrapings from the host are spores or not, depends upon whether these apparent fragments of hyphae are definitely differentiated or whether the process is a simple fragmentation of the hypha. Sabouraud considers them to be fragments of hyphae incorrectly called spores. Castellani considers that sporoid mycelium is a more correct expression than spores.

The principal characteristics of *Epidermophyton cruris* are that the fungus does not affect the hair and that it does not produce suppuration. Cultures on the Sabouraud medium are very faintly yellow at first, this color later becoming more pronounced. Sabouraud describes it as that of a half-ripe lemon. In cultures protected from light this is more marked than in those grown in full light. All are rather powdery with delicate rays at the circumference, and comparatively early (3 or 4 weeks) they show the pleomorphic transformation evidenced by tufts of white duvet.

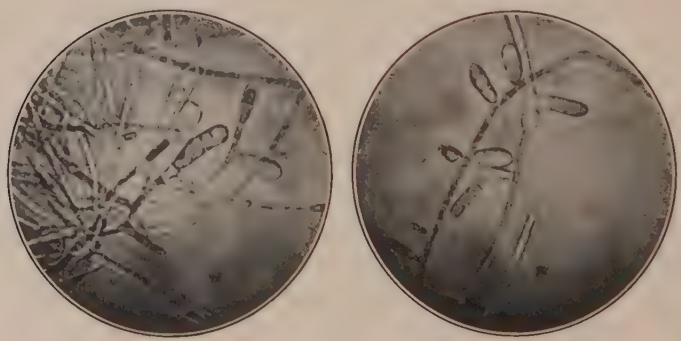
In slide preparations from cultures and in hanging drop cultures, *Epidermophyton cruris* is characterized by its



Case #58. Photomicrograph (x430) From four day old hanging block preparation. (M. audouini)



Case #198. Photomicrograph (x430) From four day old hanging block preparation. (T. asteroides)



Case #199. Photomicrograph (x430) From four day old hanging block preparation. (E. cruris)

PLATE NO. IV

fuseaux and chlamydospore formation (Plate IV) and the absence of microconidia, such as are found in the *Trichophyton*. The chlamydospores are not characteristic taken alone, as they are found in other genera; but their presence in abundance in association with the characteristic fuseaux gives them confirmatory value. The fuseaux are small club-shaped or pear-shaped structures about 9 microns in diameter, with varying lengths, septate at times, perhaps according to their age, and having no definite number of divisions. Their walls are not dense as compared to the fuseaux found in *Microsporon*. There may be found several arising from the the same stem, a condition which is unusual in other genera except *Microsporon* (*M. fulvum*). We have also observed in *Epidermophyton cruris* a spear-head shaped terminal conidium with dense walls averaging 15 microns in diameter, which we have not seen in other genera. Sabouraud says that microconidia are not found in *Epidermophyton* and Castellani mentions their rarity. We have never seen them in our cultures.

It is therefore comparatively easy to distinguish *Epidermophyton cruris* from the *trichophytons:* (1) By culture, which does not closely resemble any Trichophyton, and (2) by morphology: In *Epidermophyton cruris* the chlamydospores are usually many; in *Trichophyton* they are not so common. In *Epidermophyton cruris* the fuseaux are many and characteristic, and in *Trichophyton* they are not numerous. In *Epidermophyton cruris* the macroconidia are absent; in *Trichophyton* they are present.

Laboratory Diagnosis. — Demonstration of the fungi in the skin scales and vesicles is of primary importance in the investigation of a dermatomycotic infection. Irrespective of the species of fungus present, the treatment is about the same, so that the cultivation and identification of type is perhaps only of scientific interest or importance. It is of course not unimportant that cultural identification be made, for on it, more or less, depends an accurate diagnosis. However, the morphological appearance, mode of growth, and clinical effects of each group of trichophytons show many similar characteristics. There are certain minor specific differences which point to the fact that there are a number of species.

Study of Fresh Material. — We have found that the most expeditious way to examine for fungi in a skin lesion is to remove the scales found at the advancing borders of the lesion, by gently peeling toward the normal skin or cutting off the roofs of some of the vesicles; then clearing with a solution (15 to 40%) of sodium or potassium hydrate. Crush

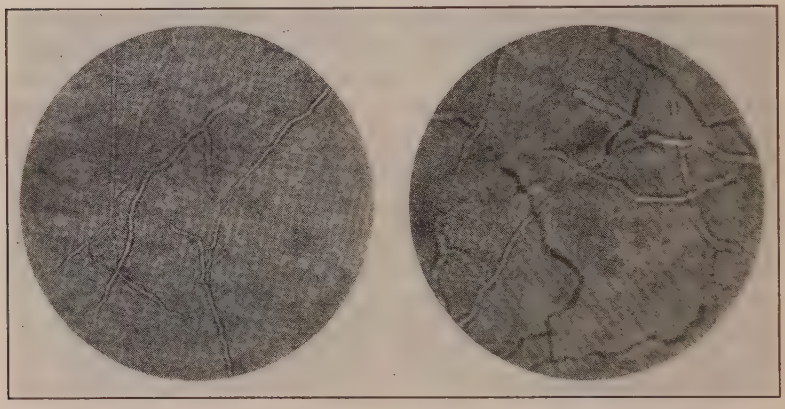


PLATE NO. III.

SODIUM HYDROXIDE PREPARATION FROM VESICULAR SKIN LESION, SHOWING THE MYCELIA. PHOTOMICROGRAPH X420.

between 2 glass slides or press down with a vaselined coverglass. Not all the scales or vesicles examined will show the parasite, and the number of hyphae or mycelia seen does not seem to bear any relationship to the severity of the infection. One of our foot cases of 20 years' duration (*Microsporon audouini*) shows the fungus almost constantly present when new crops of vesicles appear. Exudate material and eczematoid crusts are of no value in diagnosis, as the organism is seldom found in this type. Tribondeau's method[1] of treating the material with ether, then with alcohol and finally with water to remove the fat, and mounting in NaOH solution, gives a satisfactory preparation and eliminates the error that may creep in of confusing the fat globules with mycelial fragments.

The microscopic examination is made first with the low-power lens when the mould can frequently be picked up and

[1] STITT, E. R., "Practical Bacteriology, Blood Work and Parasitology"; 7th Ed., 1923, p. 208. *P. Blakiston's Sons and Co.*, Phila.

further examined by switching to the high dry lens for more detailed study. It requires up to 30 minutes for the specimen to clear, in the 15% NaOH solution; and if more rapid clearing is desired, 40% solution may be used. The light should be regulated by closing down the diaphragm and an examination should be made of all levels of the preparation, as the scales vary considerably in thickness. Positive preparations will show the mycelial filaments which branch irregularly and are broken up by septa at intervals of varying length, often resembling chains (Plate III). Short, rounded mycelial fragments resembling spores can be seen, but diagnosis should not be made on these alone.

For permanent mounts lacto-phenol is satisfactory, as it clears rapidly and can be ringed with cement to prevent evaporation. These preparations will keep for 6 months or longer.

Cultivation of the Fungi. — The best media for isolation are those of Sabouraud. Before inoculation, the material is placed in 60% alcohol for 1 to 2 hours to kill bacteria. Moulds withstand this treatment. The material is then washed with 0.9% saline and cut up into very small fragments. Agar slants and small Erlenmeyer flasks containing about 1 cm. of agar on the bottom, are inoculated with a platinum loop. Moisten the loop on the surface of the agar slant, touch the material with the loop, and transfer to the medium. Four or five inoculations are made on each slant or flask and incubated at room and incubator temperature. Recently, in addition to Sabouraud media, we have obtained primary cultures on Currie's medium and find it useful in the early elimination of the saprophytic moulds. A double sugar-tube containing lactose and saccharose, and another containing mannite, are used.

Hanging block cultures are useful in identification of the various fungi. The hollow ground slide is sterilized by flaming and the concavity filled with melted agar (Sabouraud's). The surface is then inoculated from the colony to be studied and covered with a sterile (flamed) coverglass. Another method is to spread a drop of the melted agar over a sterile coverglass, inoculate the film and adjust over a concave slide. These methods are excellent in bringing out the mode of fructification of moulds, which can be studied satisfactorily under the high-power microscope.

Staining methods are of little use in demonstrating the fungi. They are time-consuming and uncertain in their results. The fresh preparation is much more satisfactory.

COMPLEMENT FIXATION

The close connection of the capillary loops in the papillae of the skin with the vesicular lesions of epidermophytosis, and the fact that the vesicular contents consist in part of leucocytes, led us to believe that there might be amboceptors formed in response to this infection, and we have attempted to demonstrate these bodies by means of the Noguchi technique of the complement-fixation test, using antigen prepared from moulds isolated from individual cases. We do not think that even though antibodies were found in these infections, their demonstration would be of much assistance in diagnosis. Owing to the fact that in allied infections, those by *Sporotrichum* for example, antibodies are formed, we thought it would be of interest to see whether they were probably formed in infections of this nature.

Patients with mould infections for variable periods up to 24 years were used. The results in all cases were consistently negative, both homologous and polyvalent antigens being used. These findings agree with Widal and Abrami[1] who

RESULT OF COMPLEMENT FIXATION IN HAND AND FOOT MYCOSIS.

No.	NAME	TYPE OF LESION	LOCATION	DURATION	TROP. DUTY	FUNGUS demonstrated	CULTURE	COMP. FIXATION
1	R.C.	VES. & HYPER.	FEET	5 MO.	NONE	+	—	—
2	H.W.	INTERTRIG.	TOES	6 MO.	NONE	+	—	—
3	J.B.	INTERTRIG.	TOES	7 YRS.	NONE	+	—	—
4	T.F.	INTERTRIG.	TOES	6 YRS	NONE	+	—	—
5	M.C.	HYPERKERAT.	H & F	5 YRS	YES	+	—	—
6	W.C.	VESICULAR	ARCH	18 MO.	YES	+	+	—
7	M.M.	INTERTRIG.	TOES	18 MO.	YES	+	+	—
8	DR.B.	VES. & SQUAM.	HANDS	10 YRS.	YES	+	O	—
9	DR.C.	VESICULAR.	FEET	24 YRS.	YES	+	+	—
10		T. VERSICOL.	BODY	2 YRS.	YES	+	—	—
11		NEG. NOGUCHI	CONTROLS		NONE			—
12		POS. NOGUCHI			NONE			—
13		NEG. NOGUCHI			NONE			—

CHART NO. IV.

[1] WIDAL and ABRAMI, *Ann. d. l'Inst. Pasteur*, 24, I, 1910.

were unable to demonstrate the presence of antibodies in mycotic infections.

The antigens were prepared by rubbing up the heavy fungus growth from an agar slant in a mortar with about 15 cc. of absolute alcohol. This was placed in a water bath at 56° C., left for 30 minutes, and shaken frequently. This was then centrifuged until clear, and alcohol was decanted and discarded. To the residue were added 10 volumes of ether, and the mixture was shaken for 1 hour. It was placed in the dark for 24 hours at room temperature. Ether extraction was decanted and the mixture was dried thoroughly. The dried mould was then pulverized in a mortar and taken up in 0.9% saline in the proportion of 1:200. This was heated to 80° C. for 1 hour. The resulting antigen had the turbidity of about 1,000 parts per million (silica) and smears showed a uniform granular appearance under the high dry lens.

One of the charts shows the results of some of these tests upon infected individuals. (See Chart IV.) The patients whose parasites furnished the antigen used in these tests showed no evidence of amboceptors in their own sera for their particular strain. It is needless to say that all the other sera gave negative results. There was no way of testing the antigenic power of the mould extracts used as antigen. The controls were syphilitic antigen-controls and all were negative. These results square with the symptomatic recurrence and chronicity of epidermophytosis.

Agglutination tests gave consistently negative results.

Experimental animals have not been used in this study.

The cultures so far identified in this group of cases are the *Epidermophyton cruris*, *Microsporon audouini*, and *Trichophyton asteroides*.

TREATMENT

One drawback to adequate treatment of this annoying and chronically recurring condition is a failure on the part of physicians and dermatologists to appreciate a few simple points in its pathologic anatomy, and in the probable life cycle of the organisms causing it. As stated above, the organisms are best found in the dome of what we have chosen to speak of as the initial lesion, namely, the vesicle. The

little colony, spreading perhaps from one of the resistant forms, grows out in the epidermis from this point and when the vesicle is ruptured the remains of the colony are still there and the hyphae will have grown to a considerable extent out into the area surrounding the vesicle. Some of these moulds produce spore-like bodies or seeding bodies in culture, and it is reasonable to suppose that a resting stage after the active vegetative condition also occurs in the epidermis, so that the area infected may be compared to a plot of ground in which a crop has been grown and seeds of the crop have been in some cases retained in the earth.

The resting forms are held splinted, so to speak, in the epidermis. Until the epidermis which holds them is desquamated this resting stage will remain in the soil, and when conditions are favorable for its vegetation it will again sprout into life with the production of new lesions. In the older lesions, that is to say, the hyperkeratotic and intertriginous ones, the spore-like bodies of the resting stage are very difficult to demonstrate. They are nevertheless there, at least bodies which we take to be these are present in the lesions of the type described, when one carefully examines for them in sodium or potassium-hydrate solution. Another thing which makes it more evident that the mould is the cause of these lesions, is the fact that persistence in the local treatment of the lesions by medicines which will destroy the mould, will generally cure the lesions. In the hard lesions, the organisms are protected, as intimated by overlying epidermis, in many cases greatly thickened, and it is useless to try to destroy them until this hyperkeratosis has been gotten rid of by agencies which will soften the epidermis and enable the antiseptics to get at the mould.

In our experience the resistance of the resting stage of the organisms causing epidermophytosis is not very great. This is only an opinion and is not backed up by experimental work on the subject. We think so because cultures of these moulds die out rather readily. The resisting stage is not comparable to the spore of the bacterial cell, which is heat-resistant. By reason of the tendency of the lesions to recur, and because of their eczematoid appearance, the opinion is prevalent among certain dermatologists that soap is a bad thing in treatment. Perhaps in forms of ordinary eczema,

soap is *not* good, but for these mycoses it has been our experience that this teaching is unsound. It would seem that the matter of treatment resolves itself into the question of persistence in the use of agencies which will destroy the organisms until all the seeds, the resting forms, are desquamated and killed. The fact that women are less affected by epidermophytosis of the hands and feet than men are, is explainable on the basis that they are usually more careful in attention to their skin. They are certainly open to infection to the same extent as men are.

In speaking of the treatment and etiology of mycosis of the hands and feet we are speaking, not from the standpoint of the dermatologist nor of the mycologist, because we have no special knowledge along either of these lines. We are speaking from the standpoint of physicians who have had personal experience with epidermophytosis, and with this understanding we have found the following preparations to be best in the treatment. For the vascular lesions the procedure is to clip off the top of the vesicle and release its contents. This open vesicle should be painted thoroughly with a good tincture of iodine which destroys the organisms released in the fluid and sterilizes the base of the opening and the surrounding area. This applies to vesicles on the hands and feet and to other lesions on the surface of the body. Tincture of iodine as mitigated according to the character of the skin is one of the best treatments that we have for epidermophytosis of the crutch and axilla. Its disadvantage with respect to the hands is that it stains.

For the lesions which are pus-infected the best treatment we have found is that first used by Greenwood[1] and later by Feldman and Ochs[2], *i.e.*, varying strengths of permanganate of potash. This drug not only destroys pus-infection but seems to have a specific effect upon the mycotic organisms themselves. It is an excellent form of treatment for lesions on the hands, and the stain produced by it may be very quickly obliterated and the action of the drug stopped by means of another mild parasiticide. This latter is peroxide

[1] GREENWOOD, A. M., "Epidermophytosis"; *Boston Med. and Surg. Journ.*, Vol. 187, No. 5, pp. 176–180, Aug. 3, 1922.

[2] FELDMAN, S., and OCHS, B. F., "Potassium Permanganate as a Curative Agent in Dermatologic Diseases"; *Arch. Dermat. & Syph.*, 6:1922, p. 183.

of hydrogen, to which has been added 1 part in 5 of U.S.P. strength of acetic acid. Washing with this solution of peroxide destroys entirely the stains of the permanganate of potassium. As soon as the permanganate stain has been removed by the acid peroxide of hydrogen, this latter should be washed off with plain water. Both of these agencies are oxidizers and after a treatment of this sort a local application of lanolin, well rubbed in, tends to prevent any hardening of the epidermis, which comes from the stronger permanganate solutions.

A preparation which we have found of very great use in the treatment of this disease, particularly the lesions on the hands and feet, is the U.S.P. preparation, *Linimentum saponis* (soap liniment). This is a solution of soap, camphor and oil of rosemary in a mixture of alcohol and water. It is ordinarily employed for massage and for joint affections, and we have not previously heard of its being used as a treatment for mycotic infections. It may be applied to the hands and feet at night on going to bed, care being taken to massage it into the interspaces between the fingers and toes until it is dry. Left on over night, it seems to change favorably the reaction of the perspiration. It leaves a small amount of camphor, which is an antiseptic on the skin and is easily washed off when the morning bath is taken. The soft lesions, that is, soft corns and open vesicles which have been treated with tincture of iodine, are quickly healed under this treatment. As this preparation is easy of application and easy of removal, it is one of the best preparations with which to treat the soft lesions caused by moulds. It tends to keep the skin soft, which is one essential of a permanent cure.

Those drugs which produce necrosis of the epidermis, such as salicylic and benzoic acid (Whitfield's ointment) in our experience are rather disappointing. The tendency to recurrence of the lesions of epidermophytosis, above spoken of, which we think is explainable on the basis of imprisonment in the skin of the resting forms of the organism, may be compared again to an agricultural field and the treatment to the burning of that field. One burning may destroy many of the seeds but it does not destroy all. Some of them are imprisoned in the earth and will ultimately spring into life.

The continued treatment may be likened to repeated burnings of the same area — enough application of fire to the field will render it sterile. So with the treatment of this condition by mild antiseptics such as those indicated; the long-continued application will result in sterilizing the skin of the seeds. We would then classify the agencies of greatest use in treatment: (1) Soap liniment and careful attention to manicuring; (2) The judicious use of permanganate of potassium and its adjuvant, an acid solution of hydrogen peroxide; (3) The use of a bland ointment, and the best one in our experience is plain lanolin; (4) As a supplement to all three, tincture of iodine. The careful and prolonged use of these preparations will, in most cases, accomplish a cure.

The use of light and X-ray to treat *epidermophytosis* is unnecessary, except perhaps for ringworm of the hair and nails. It takes the services of 3 or 4 people to do what the understanding patient can intelligently and effectively accomplish at home. It is like using a 16-inch rifle to shoot a squirrel out of a tree.

"PINTA" OR "CARATE"

(With Special Reference to Treatment)

EDUARDO URUETA, M.D.

SYNONYMS, DEFINITION, HISTORY AND GEOGRAPHY

The disease which Unna has latinized by the name of *Pinta cerulea* is named in Colombia and Venezuela *carate*, and in Mexico *tiña;* being more widely known in the medical world by the name of *pinta.* This is a group of tropical *dermatomycoses* caused by various species of fungi of the genus *aspergillus*, *penicillium*, *monilia*, *montoyella*, and similar forms that live and grow in the superficial coats of the skin, where they produce variously pigmented patches strongly contrasting with the surrounding uncontaminated epidermis.

The disease seems to have existed since times remote, as the history of the Aztecs mentions it; but only from the eighteenth century does it appear in the medical writings, Polanco in Mexico being one of the first who mentioned and described it (1760) and later on Juan de Valazco in Colombia (1780). However, it was the Frenchman, Alibert, who in 1829 made a more elaborate study of the disease, describing it by the name of "*tache epidemique de las cordillers.*" Gastambide discovered the fungus which causes the disease, in 1881. More recently the investigations and publications of Montoya y Flores, a Colombian, have made the disease and its fungi still better known. It is geographically distributed in Tropical America, viz., Mexico, Central America, Colombia, Venezuela, Peru, Chile and Brazil, being limited in each of those countries to certain sections, while outside of these, the disease does not exist.

In Colombia, for example, it is to be found only in the provinces of Magdalena, Antioquiam Cauca and Northern Santander; in Venezuela, in the Province of Lara (Barquisimeto); in Mexico, in the provinces of Tabasco and Michoacan.

ETIOLOGY

Montoya y Flores has found more than 20 different fungi as causative agents in producing the various hues found in the skin of caratosos.

Scrapings from the diseased area, examined in liquor potassæ, show mycelial threads with shorter and thicker branches, which end in fructifications of various types. Cultures of these fungi on Sabouraud's medium, at a temperature of from 30 to 40 degrees Centigrade, are not difficult to obtain. The fungi can be classified after their fructifications and biological properties.

There have been found several species of *Aspergillus* in the violet, violet-black, pure blue, bluish, and red varieties, of which the best known is *Aspergillus pictor Blanchard.* On maltose agar it grows first whitish, to change afterwards to a greenish, violet or greenish-violet colour.

Several species of fungi show fructifications which are to be classified between *Aspergillus* and *Penicillium.* The presence of *Penicillia* was established in the greyish-violet carate. The most important is *Penicillium montoyai Castellani* (1907) the cultures of which are of a dark greyish colour.

In a case of white *carate* was found *Monilia montoyai Castellani* (1907) growing on sugar media with creamy white colonies. *Montoyella nigra Castellani* giving black cultures occurs in one variety of black *pinta; Montoyella bodini* cultures growing with whitish or greenish colours in a red variety.

The fungi affect the epidermis, especially the corneous layer; but there may be changes in the rete Malpighii and also in the corium. In later stages pigment cells are more or less destroyed.

According to the mentioned biological properties of these fungi, it is natural to ascribe to the mere presence of the fungi an important part in the origination of the colour of the affected patches, but at the same time, the changes the skin undergo are also important. In the classical cases of dull-white *carate* the corneous layer, as well as the *rete Malpighii* and the corium, is to a very marked degree free from pigment; in more or less extended areas there is no pigment at all, while in the surrounding areas this vitiliginous

condition is intermingled with normal or hyper-pigmented spots, some of which may remain in the interior of the vitiliginous area. They are often around a hair, and show large quantities of pigment, even in the most superficial layers of the epidermis. The superficial scrapings of black or blackish forms of *carate* show marked pigment, in contrast with those from white cases.

After the clinical examination of one case of red *carate* that we saw, we are inclined to believe that the main causative factor of this particular colour consisted in changes in the structure of the epidermis and corium, the spots giving, at scraping, comparatively large scales that left beneath them a slightly bleeding surface, which we did not see in the other varieties.

In the dull-white *carate*, microscopically we very seldom found fungus-elements, whereas in cases of black or blackish *carate* there were striking quantities of mycelia and spores, the largest number of them in a marked, greyish desquamating spot found at the edge of a diffuse blackish area of the face.

PREDISPOSING CAUSES

Heat and humidity are the conditions required for life and growth of the parasite. These climatic conditions, together with uncleanliness of the labourers, and the abrasions caused by the kind of work they undertake, bring the fungi to the skin and open the door to the infection.

Insects that are bred in stagnant water, in places where the disease is endemic,— especially the sand fly — are thought to be the ones that inoculate the spores of the fungus. My personal experience induces me to believe that the rôle of these insects is doubtful, as I have seen white foreigners and well-to-do natives remain immune though they have been exposed for many years to the bite of these insects in the worst sections of the country. It is therefore more likely that the slovenliness and the hard work among the manual labourers play the more important rôle in the contraction of pinta.

As it is not known how and when the infection takes place, we do not know the *incubation period.*

SYMPTOMATOLOGY

The patches start in the forehead, between the brows, the *alæ nasi*,—with more or less pruritus, according to the variety that causes the infection, following in this order of frequency:— the hands, feet, (in the person who goes barefooted) sides of the neck. If allowed to go on without treatment it spreads to the other uncovered parts of the body, and it is seen in some careless natives to be invading almost the whole body. The other regions lastly involved are the legs, the front of the thorax and abdomen; and, though very seldom, the back or such parts of the body that the individual scratches with difficulty.

The patches are small at first, of the size of a few centimetres; then gradually increase occupying spaces of the width of several inches, and forming irregular and capricious figures with festooned margins.

I remember a case in our hospital, a man whose abdominal skin, capriciously spotted, formed figures so queer that a tourist who happened to see him expressed her sorrow for not being able to get a hand bag made from such a picturesque hide.

The chromatic scale of the varieties goes from the yellowish-violet, blue, and black, which are the more frequent, to the red which is less frequently seen in Colombia, until it reaches the dull white which is the last stage of the disease. The violet is very common, but the greyish-violet variety is still more common than the pure violet. The red variety, which is very rare, is met with more among strangers and natives of fair complexion than the other varieties, and its appearance is in the same order. It often happens that the dorsum of the hand is invaded by the *Montoyella bodini*, which is the fungus that produces the red variety. This gives more pruritus than the other varieties.

Regarding the pure-yellow form to which other authors refer, I have not seen it. The so-called white variety represents only the last stage of the *pinta* as in that of other fungus dermatoses like the *tinea flava*, *tinea alva*, when the fungi have more or less disappeared after destroying the pigment.

The authors describe certain atypical varieties, which are rather complications of the *carate*, and which may coincide with the *tinea impetigo*, *lichen* or other derangements of the skin, parasitic or otherwise.

Regarding the disappearance of the disease after an attack of small-pox, it has not been observed by me in spite of my having seen *carate* with small-pox. This phenomenon is said to be due to the high temperature of this exanthema, although the same effect is not attributed to other hyperpyrexias.

DIAGNOSIS

The diagnosis is easily made in places where the disease is endemic,— by the simple ocular inspection of the characteristic stains; of course, provided that one has some experience with the condition. In places where the disease is unknown, the diagnosis of *pinta* will give place to doubts, when it will be necessary to resort to a microscopic examination of the scrapings of the patches, duly prepared, which will decide the question. Apparently *carate* may be confused with some *tineas*, as *tinea alba*, *tinea nigra*, *tinea flava*, but in these the trichophyton or other fungi will be found with the microscope.

With certain forms of anesthetic leprosy, the difference is so marked that it is rather difficult to mistake the one for the other.

THE PROGNOSIS

The prognosis of *pinta* is favorable, for the reason that it does not kill or greatly annoy the affected party; but it is serious, in that it is hard to cure and requires for its proper treatment a good deal of care and attention. The only inconvenience is caused from its unsightliness, about which the low type of natives, who are nearly the only ones affected, do not seem to care.

TREATMENT

My personal experience leads me to favor *Chrysarobin* among all the medicines that have been recommended. I consider the *Chrysarobin* treatment as efficacious for *pinta* as for ringworm.

Chrysarobin is a mixture of neutral principles extracted from the Goa powder, a substance found deposited in the wood of *Vouacapoua Araroba*.

The British Pharmacopœia recognizes under distinct

headings crude *Chrysarobin* (Goa powder or Araroba), and the purified *chrysarobin*, which is the one recommended.

Chrysarobin is between a brownish and an orange-yellow, micro-crystalline powder; tasteless, odourless and irritating to the mucous membrane. It is almost insoluble in water, but very soluble in chloroform and ether. Hesse found that *chrysarobin* is a complex body consisting of at least 5 different substances, viz:— chryso-phanol-anthranol, its methyl-ether; emodinol, and its methyl-ether, and chrysarobol. Chryso-phanol-anthranol is the one to which are due the characteristic qualities of the drug, according to Tutin and Clewer. When it is taken internally in sufficient amounts, *chrysarobin* has been pronounced as a gastro-intestinal irritant giving rise to large, watery, brownish stools and vomiting. It is only externally used.

Though it has had extensive use in South America for skin diseases, it is only since 1874 that it has been well known by the medical profession, after the studies of Fayrer.

Schamberg, Kolmer, and Raiziss in an elaborate research on its mode of action reached the conclusions that *chrysarobin* is without germicidal properties, and that its beneficent effects are probably due to its chemical affinity for the keratin elements of the skin, the drug abstracting from the epithelium the oxygen for its oxidation, which takes place simultaneously with this union.

When applied over the skin it produces irritation, itching, and a burning sensation; applied externally to the skin in very strong mixtures, it may provoke albuminuria and fever. It is eliminated by the urine, which becomes brown. It requires care in handling, for it stains the clothes. (U. S. P.)

The best manner to apply it is in a solution with collodion in the proportion of from ½ to 1 dram of *chrysarobin* in 1 fluid ounce of the official flexible collodion. Some dermatologists apply it in a solution of chloroform in the same proportion as that for collodion, covering it right afterward with a thin coat of *traumaticina* (gutta-percha 5 grams, chloroform 80 cc.). My personal procedure is as follows:—

After removing all the crusts from the affected skin, by the ordinary measures, I apply over the lesions with a camel's-hair brush this preparation:— *Chrysarobin* 5 grams;

gutta-percha 5 grams, chloroform 80 cc. If the local reaction is too strong, I decrease the proportion of *chrysarobin*. This varnish should be renewed daily by means of new coats being applied over the preceding coats, unless this medical dressing gets soiled, in which case it will be necessary to remove it with benzene or ether and apply a fresh coat.

Of course, it is necessary, for the success of the treatment, to watch closely the irritant effect of the applications over the skin, in order to increase or decrease the proportion of the active substance or even discontinue it temporarily in the case that a *medicamentosus dermatitis* takes place.

The large patches have to be treated in parts, and not many at the same time, to avoid the absorption of the drug which is injurious to the kidneys, mainly in children.

The *chrysarobin* — which is so efficacious for attacking and destroying the fungus in the coats of the epidermis, superficial and deep, even in the *rete malpighii*,—has no action over the so-called white variety when the fungi have disappeared after destroying all the natural pigment of the skin.

It has been while the disease was in this incurable achromatic stage that I have tried the tatooing by means of some coloring preparations. It must be understood that great accuracy in preparing the color is necessary, to imitate exactly the hue of the skin of the individual.

I have used the tatooing with good results upon natives of dark skin, by using solution of *sepia* duly sterilized, in concentrated proportions according to the shade to be reproduced. To perform this "inlaying," I use the ordinary instrument that serves the oculist, for tatooing the cornea in extensive leucomas, which consists of a bunch of needles bound together in the form of a brush.

Here also as with the application of the varnish of the *chrysarobin* it is necessary to go on tatooing small portions of the skin at a time, inasmuch as the reaction from the needles is still more pronounced than from the *chrysarobin*. This artificial manner of colouring the skin in the white *carate* is the only way to deal with the ugly looking dull-white patches, that have the tendency to remain for life.

Regarding prophylaxis: Personal hygiene and cleanliness of the surroundings is the fundamental requirement for

avoiding this decorative condition. I am glad to note that on the Atlantic coast of Colombia, which has been one of the classical locations of the *carate* in its purest form, it is gradually disappearing; and with the continual furtherance of sanitation, the day is not far distant in which *carate* on that coast will be an oddity.

DISCUSSION

Dr. Aldo Castellani (Opening the Discussion).— I really do not think I am competent to discuss the subject of *carate*, because I have never been in countries in which the disease is endemic. My investigations have been carried out on 2 or 3 imported cases, — and I think that when you want to thoroughly investigate a disease, it is always advisable to go into the country where that disease is actually endemic. I hope to see numerous cases in Honduras and other countries of Central America, and then I shall perhaps be in a better position to discuss the matter.

I will limit myself therefore to expressing my great admiration and my deep congratulations to Dr. Urueta for his most interesting paper.

Dr. Friedrich Fülleborn.— I would like to ask Dr. Urueta whether he has seen in Colombia cases of *pinta* in which the colored skin was not dry, but wet and foul. According to some text-books on tropical medicine, one would think that the latter form, making the patients unfit for human society because of the foul odor, is the usual form of *pinta*.

Lieut.-Col. James Cran.— In British Honduras, *pinta* is a very common disease among a certain race of people, namely the Caribs, who live in considerable numbers in the Colony. These Caribs originally came from St. Vincent. As I said, *pinta* is exceedingly common among them — I don't know the percentage of cases, but should say 50% of the adults have it. It is much more common among the women than among the men, and I think this is because the women are the agricultural laborers, and the men the fishermen. The commonest site for the disease among the women is on the hands and feet. It begins as the dark-blue or black variety, and finishes up as the white variety. We very seldom get an opportunity to treat it because it is so common that they cannot "throw stones at each other"; the disease causes them no inconvenience, — so they disregard it. Occasionally they will come and ask to be cured, but all that we can do is to stop the spread of the disease, and when they find that we cannot get rid of the spots they give up in disgust.

Several years ago a doctor inoculated himself on the forearm with this disease, by means of scrapings. I do not remember what the incubation period was, but it was a short one. He cured himself with *chrysarobin*. I have lately tried the treatment, recommended by Dr. Castellani, with considerable success. It was introduced to me by Dr. Castellani's colleague and a friend of mine, Dr. Newham, and I have had more success with it than with any other treatment.

Dr. Eduardo Urueta (Closing the Discussion of His Own Paper). — I wish to thank Dr. Castellani, who has discussed the subject with his exceptional knowledge of fungi, and also Dr. Fülleborn and Dr. Cran for their interesting remarks on this subject. In answer to the question as to whether I have ever seen "wet" cases in Santa Marta, Colombia, I may say that I never have.

My paper is principally concerned with the treatment, urging the use of *chrysarobin*, applied as a varnish, instead of the usual anti-fungus medicines such as salicylic acid, resorcin, iodine and mercury, and also to recommend the tatooing for the incurable white patches of the last stage. A cure for these white patches is of the keenest interest to the practitioner in that locality, as these unsightly markings are the most humiliating part of the disease for the wealthy native planters and their families. I shall be satisfied if this talk on *pinta* stimulates investigation toward that end, — and be sure that in Santa Marta you will find a rich field for such research, a cordial welcome, and all the help we are able to give.

A REVIEW OF AINHUM, WITH RADIOGRAPHIC DEMONSTRATION OF ITS BONE PATHOLOGY

A. A. Facio, M.D.

While some of the observers hold the opinion that ainhum is possibly a very much attenuated form of nerve leprosy, others have suggested that it is a trophic nerve lesion dependent upon some nervous affection, and still others believe that it is due to the wearing of rings and other tight adornments which are worn around the toes, and which are so much in vogue with the primitive dark races and their descendants. The majority of investigators and observers disown those theories and agree that it is produced by a purely unintentional mechanical cause, such as the constant irritation and injury of the derma of the little toe to which the flat bare-footed (Figure No. 1) dark-skinned natives are naturally subjected.

Manson's own impression, supported by several others, is:

> that it is provoked, at all events in the first instance, by wounds so easily inflicted on bare feet in walking through grass and jungle, and which through constant irritation, produced and kept up by wounds from sharp grasses and so forth, would in time give rise, especially in the dark-skinned races so prone to keloid, to fibrotic changes of the derma, which might very well end in a sort of cicatricial contraction, and ultimately in a slow atrophying strangulation of the affected member.

Castellani and Chalmers are inclined to believe that "the condition is of parasitic origin, the infection taking place probably through the small superficial lesion or wounds which may be found in people going barefooted."

The gross local pathology, while it resembles in a measure that of nerve leprosy and Raynaud's disease, is not by any means typical of either disease.

During the last 3 years I have seen 5 cases, and of these none has shown any lesion or symptom — other than the one affecting the little toe — that would make one think of Raynaud's disease or leprosy. It was impossible to isolate the bacillus of Hansen from the nasal secretions of any of

FIG. NO. 1.

Advanced case of Ainhum. This photograph was taken four days before the toe dropped off. Note the deep constriction around the root of the little toe and the well defined sclerotic ulceration of the derma.

these patients, even after the administration of large doses of potassium iodide.

Dr. F. B. Mallory, of Boston, to whom we referred one specimen of ainhum for microscopic examination gives the following description of the pathological histology of this disease:

> Sections show marked sclerosis of the arteries, with partial to complete obliteration of them, a little chronic inflammatory reaction and marked infiltration with mast-cells. Tubercle bacillus and Gram-Weigert stains for leprosy bacillus negative. (Figures 4, 5, 6, 7 and 8.)

From a viewpoint of investigation, it occurred to me that, if an X-Ray study of the gross pathology of the bones affected were done, some light as to its nature could possibly be obtained by comparing it with the osseous pathologic changes

characteristic of leprosy. Several pictures were taken, and Dr. Jimenez, our rœntgenologist, made the following report:

> The most striking feature of the radiographs is the almost total disappearance of the middle phalanx of the little toe, of which there is only a very small fragment left, and of the proximal phalanx only the proximal end is left at the metatarsophalangeal joint. [The soft parts show a constriction amounting to almost complete detachment of the little toe at the digitoplantar fold (Figure No. 1)]. The phalanges of the other toes, in the diseased foot as well as those of the sound foot, show atrophic changes. (Figure No. 2 and No. 3.)

It is worth noticing, in connection with these radiographs, the description of the characteristic changes of the bones in leprosy, as given by Bætjer and Waters in their book on "Injuries and Diseases of Bones and Joints," as well as the striking similarity of the radiographs which they give in their book as illustrations of leprosy with those at present under consideration. They say:

> Leprosy is characterized by a progressive atrophy starting in the terminal phalanges and gradually extending backward, involving all the phalanges. There is gradual absorption of the bone, so that it eventually disappears.

It is important to note, in connection with Dr. Jimenez' report, that the 5 cases which I have observed were all in members of the negro race, who belonged to a somewhat scattered community of the same people in which I have detected 4 cases of leprosy during the last 5 years, and this certainly seems to add weight to the supposition that ainhum may possibly be an attenuated form of nerve leprosy. Nevertheless, as it is not impossible that 2 different causes may show a very similar, almost equal, pathologic change, it is interesting to consider the disease under discussion from the standpoint of its other causal effects, as determined from the history of the case and the circumstances which surround it. I make mention of this because Manson's view seems very plausible and agrees, at least in part, with the history and development of this disease in the patients that I have studied.

All 5 patients, middle-aged, robust, and otherwise healthy negroes, are laborers in the farms, who have gone barefooted

FIG. No. 2.

Radiographic appearance of the bones of the foot in Ainhum, showing the almost total disappearance of the middle phalanx, partial disappearance of the proximal phalanx of the little toe and the atrophic changes of the distal phalanx of the little toe and all the phalanges of the other toes.

Fig. No. 3.
Showing atrophic changes of the phalanges of the right foot.

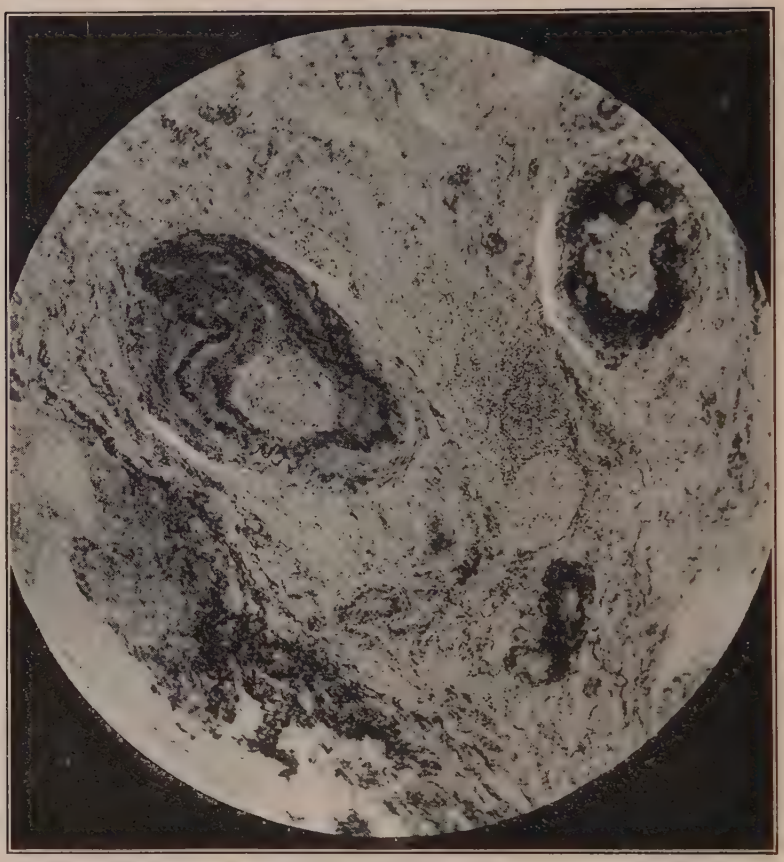


FIG. No. 4.

M 1691 (U.F.S. 25). Ainhum. Weigert elastic tissue stain showing sclerosis of arteries, increase of elastic tissue in and around them, and chronic inflammation.

part of their lives, and though they wear shoes now, they wear no stockings while at work, and the shoes are nailed and almost always old, ragged and torn, so that instead of affording protection they invite constant irritation, and soak in the intense humidity of our tropical soil.

Of these patients, only the one from whom we obtained the pictures can give a clear history of how the trouble commenced, and he states that over 5 years ago, when returning from work, he stumbled on a rock and hurt the left foot. On examining the foot, he detected a crack or

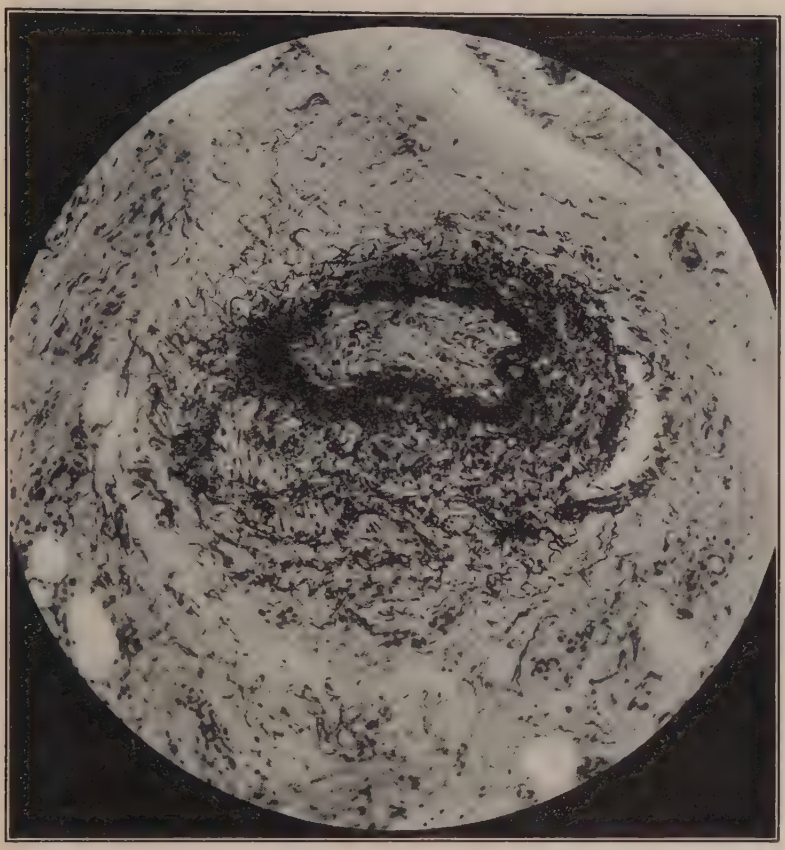


Fig. No. 5.

M 1693 (U.F.S. 25). Ainhum. Weigert elastic tissue stain. Sclerosed artery with marked increase of elastic tissue.

fissure at the digito-plantar fold of the little toe, but as this gave him no further trouble, he paid no attention to it. Even 3 years later, when the toe began to swell and the derma at the digito-dorsal line became hard and showed signs of inflammation, he was not concerned, for the lesion did not molest him in the least.

This patient came to the hospital on July 8th, 1922, not because he experienced discomfort or pain, but because, as he said, "he did not like the looks of the toe." At this time the lesion exhibited the characteristics of an advanced

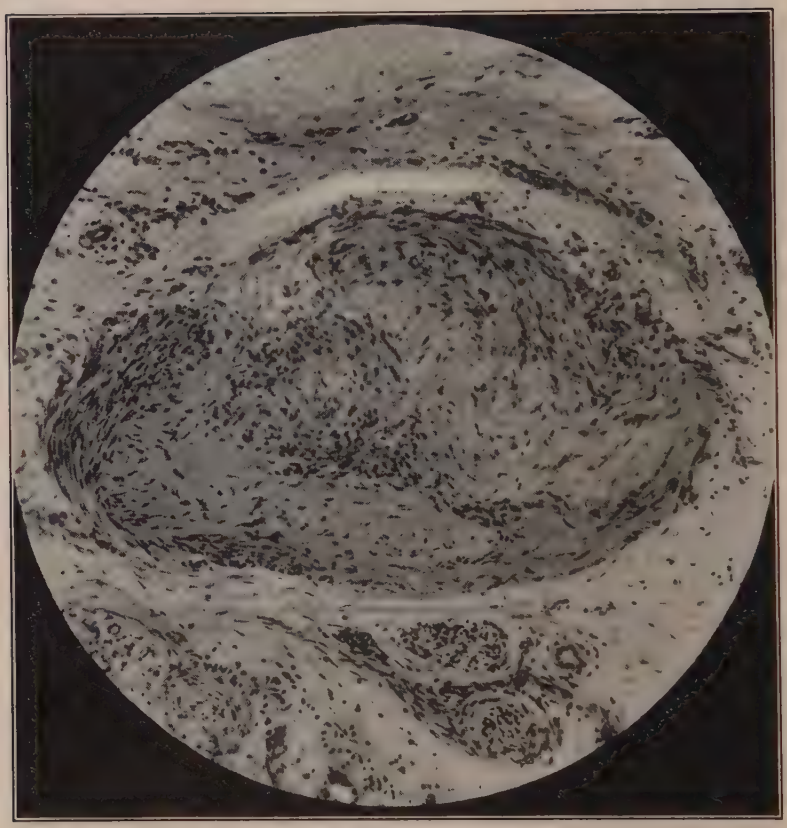


FIG. No. 6.

M 1694 (U.F.S. 25). Ainhum. Hematoxylin and eosin stain. Marked sclerosis of artery.

case, viz., a deep constriction around the root of the little toe, which remained attached to the foot by merely a few muscular fibres. It was swollen, globular in shape, and of a dead purple hue, and the skin just above the digito-dorsal line was very hard, sclerotic, cracked and ulcerated (Figure No. 1). I could manipulate the toe as much as I wished without causing the patient the least pain. The toe dropped off spontaneously four days after, and the ulceration healed rapidly, leaving a very clean scar.

That the disease causes but little discomfort and practically no pain, is proved by the fact that 3 of these cases have come to the hospital when the toe was just ready to drop off.

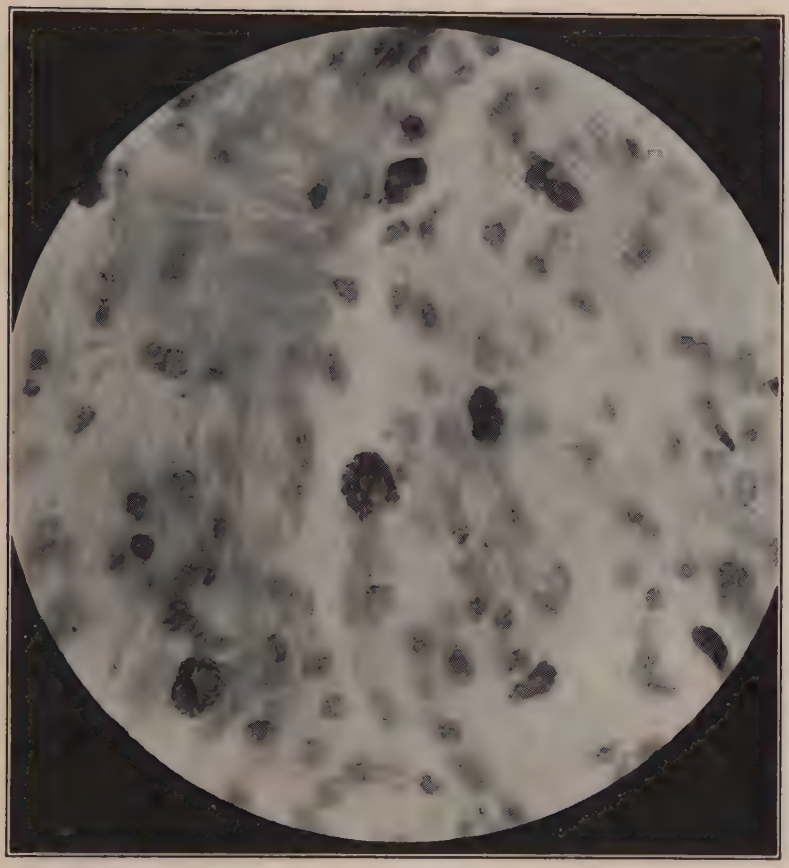


Fig. No. 7.
M 1697 (U.F.S. 25). Ainhum. Mast cells present in large numbers all through tissue.

Manson tells us that "if we examined the under surface of the joint flexures of the toes in many individuals of this race, even of those not affected with ainhum, we often found the skin, particularly at the proximal joint of the little toe, thick, rough, scaling, and sometimes even ulcerated." Not only have I observed this, but also in several individuals I have examined, the skin in those places is so rough and indurated, especially in those who wear shoes, that the edges are almost as hard as the cut edges of a quill, giving rise to, as Unna describes it, "a linear scleroderma, in which the

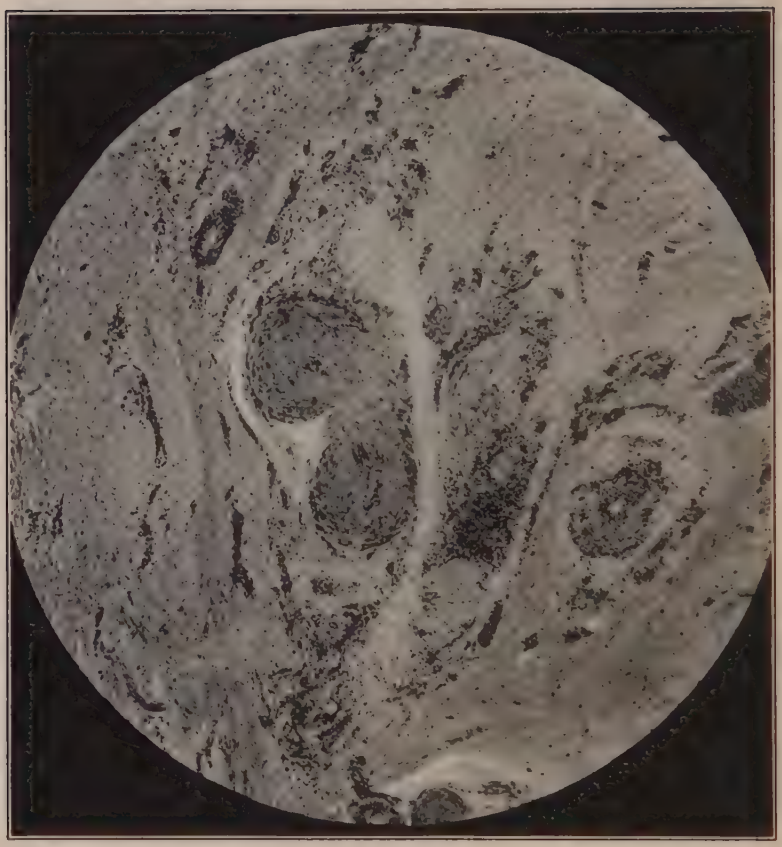


FIG. No. 8.

M 1690 (U.F.S. 25). Ainhum. Hematoxylin and eosin stain showing sclerosis of arteries and chronic inflammation.

epidermis hardens and shrinks, compressing the papillary layer and causing pressure necrosis." This eventually cuts off the blood supply of the distal portion of the toe, which as Castellani and Chalmers put it, "therefore becomes œdematous and fatty, while the bones undergo rarefying osteitis, so that the digit is gradually separated from the foot, a process which takes place through the bone of a phalanx," as can be seen in Figure No. 2.

The above pathologic process, it seems obvious, operates in the same fashion as would a mechanical contrivance, such

as a tight ring around the toe, and no doubt it is responsible for the supposition that such articles are the cause of this disease.

One thing that is certainly baffling, at least to me, is why, if similar and even equal amount of sclerosis is found on the other toes, the disease practically always affects the little toe only. The reason for this possibly lies in the anatomical position of the latter, which exposes it to much more constant irritation than the others.

Notwithstanding the fact that Manson's view, supported by others advanced, seems the most logical, it is of interest to consider the possibilities which a trophic nerve lesion may have as a cause of ainhum, and while I speak of this only from an hypothetical point of view — inasmuch as I have always failed to find such a lesion — if we examine the X-Ray pictures attentively it will be observed that while the middle phalanx has almost totally disappeared, the proximal, which is above the constriction has partially disappeared also; the distal, though it is below the constriction and shows rarefying osteitis, still remains complete and retains its normal shape. Why should part of the proximal phalanx disappear, if the blood supply of the toe is cut off below it, and why should the distal phalanx remain if its blood supply is entirely cut off above it? This may have its explanation in that the constriction, owing to its proximity to the proximal phalanx, affects this in part; and while the distal phalanx stays free from pressure and its blood supply is entirely cut off, it remains practically intact for the same reason that bones in a dead body are not absorbed; and, as we may consider this a non-refutable fact, I believe that we can discard without further prejudice any theory purporting to show that a trophic disorder may be the cause of ainhum.

The fact that I have found some cases of leprosy among the same people in whom I have seen the cases of ainhum, though possibly a mere coincidence, (and irrespective of the absence of leprosy findings, barring the striking similarity of the bones affected in both diseases) led me to suspect the existence of a possible connection between the two, as suggested by others, and to keep in touch with the patients. During the last 3 years I have seen and examined 3 of the patients at various intervals and none of them have, at any

time, shown any symptoms of leprosy,— on the contrary these men are very active and are enjoying good health.

In view of this, I believe that we can, as well, safely disregard leprosy infection as an etiological factor in ainhum.

Trophic disorders and leprosy being thus eliminated as causative factors of ainhum, we are bound to conclude that it is produced, as Manson puts it — at all events in the first instance — by a purely mechanical cause; and though there may possibly occur a secondary parasitic influence in the continuation of this disease, this is, so far, hypothetical.

The treatment of ainhum is so simple that it requires but little discussion. It consists in a simple amputation of the affected toe above the constriction. It has been said that by means of a longitudinal cut into the groove, its progress may be stopped. I have failed to obtain any results with this procedure; and as, at all events, the toe will eventually become spontaneously amputated, I think it is best to amputate as soon as the diagnosis is made. The moment the toe is amputated, whatever amount of ulceration has taken place above the pressure ring begins to heal rapidly, and the patient can be discharged from the hospital without loss of time.

The prophylaxis consists in cleanliness and wearing of stockings and comfortable shoes.

DESCRIPTION OF THE PHOTOGRAPHS.

FIGURE No. 1. Advanced case of ainhum This photograph was taken 4 days before the toe dropped off. Note the deep constriction around the root of the little toe, and the well-defined sclerotic ulceration of the derma.

FIGURE No. 2. Radiographic appearance of the bones of the foot in ainhum, showing the almost total disappearance of the middle phalanx, partial disappearance of the proximal phalanx of the little toe, and the atrophic changes of the distal phalanx of the little toe and all the phalanges of the other toes.

FIGURE No. 3. Atrophic changes of the phalanges of the right foot.

FIGURES Nos. 4, 5, 6, 7 AND 8. Microphotographs showing pathological changes.

Discussion.

Dr. Aldo Castellani (Opening the Discussion).— We have been listening to an exceedingly valuable paper, and I wish to congratulate Dr. Facio very warmly. I should like to say just a few words on three points — first, the etiology of the disease; second, the geographical distribution; and third, the treatment.

1. *Etiology.*— I think we must all come to the conclusion that we know nothing definite about the etiology of this condition. Of one thing, I think, I am perfectly certain: it is not a manifestation of leprosy.

2. As regards the *geographic distribution*, we all know that ainhum was considered to be a strictly tropical disease. I am afraid that we have to transfer this disease from the group of strictly tropical diseases into the group of cosmopolitan diseases, because quite a number of cases have been reported from subtropical countries, and I have seen 2 typical cases in the Balkans and also 1 typical case in the south of Italy, in an old Italian peasant.

3. *Treatment.*— When I was in Africa I used to treat this condition by simply making a slit into the constricting band, and a very marked improvement resulted in most cases, but after a time the disease started again and sooner or later the little toe dropped spontaneously. Therefore, at the present time I am inclined to agree with Dr. Facio, that the best treatment is amputation of the small toe as soon as symptoms of this condition appear.

Dr. Foster M. Johns.— I had the pleasure very recently, in the wards of Dr. Chaille Jamison in the charity Hospital, in New Orleans, of observing a case that was provisionally diagnosed as ainhum, in which the middle phalanx of the big toe of each foot had necrosed during a period of about 2 years. I wish to ask the question as to whether this condition could be recognized as occurring in the big toe, or particularly in the toes of both feet.

Dr. Edward I. Salisbury.— I am sorry that Dr. Runyan is not here. We usually see these cases of ainhum in the surgical wards, and his experience is longer than mine. I have seen only 8 or 9 cases, and have amputated no more than 5. I have seen ainhum on both the little toes. The pathological examination of all these cases was made, and no leprosy was found. Some were ulcerated, owing to a secondary infection. All findings showed arterial obliteration. It is my opinion, from a superficial examination of all these cases, that the disease is due to callus which is caused by the patient's going barefooted over long periods of time. The

callus finally becomes very deep, and the toe atrophies from pressure applied to the blood supply.

Dr. A. A. Facio (*Closing Discussion of His Own Paper*).— I wish to express my appreciation to all the gentlemen who have participated in the discussion of this paper. To answer Dr. Johns' question, I have but to mention that Dr. Chalmers had a case in which all the toes of one foot were affected, as Dr. Castellani informs me.

SHORT REMARKS ABOUT SOME TROPICAL DISEASES IN ARGENTINE

P. Mühlens, M.D.

I. Upon invitation from the Department of Hygiene, of Buenos Aires, I had the opportunity to study, during the months of April, May and June, the diseases occurring in the northern parts of Argentine. Accompanied by my collaborators, Sta. Dr. Petrocchi, Dr. Dios and Dr. Zuccarini, I visited primarily the malarial districts in the provinces of Tucuman, Salta and Jujuy, up to the boundary of Bolivia. It was already well known that these provinces are the most strongly malaria-infected ones of the country, but the epidemiological and statistical data so far published had to be revised and completed. To make a parasitological index, we studied blood preparations from more than 7,000 persons in the different malarial districts. When we came into the malarial districts we heard that the majority of all malaria cases were tertian fevers, infections with the *Plasmodium vivax*. But our examinations showed that this opinion had to be corrected, at least during the time of our examinations at the end of summer and the beginning of autumn. In 7,024 examinations with the thick-film method, 2,331 were positive. Of these positives,

800 (34.3%) were *Pl. vivax*,
580 (24.9%) were *Pl. malariæ*,
871 (37.4%) were *Pl. falciparum*,
80 (3.4%) were mixed.

Therefore most of the single infections (more than $\frac{1}{3}$) were caused by *Pl. falciparum*. In some regions we found veritable fresh epidemics of estivo-autumnal: For instance, in a region of the Province of Salta, among the laborers of a railway construction, up to 100% were infected in some localities. It is also of interest that in some schools we found up to 70% or more of the children present, were infected — most of them with estivo-autumnal parasites.

Just as it was little known that estivo-autumnal fevers occurred in such a large percentage in the above-mentioned

provinces, it was also little known that the quartan infections also occurred in large numbers. In some districts we also found focal occurrences, with over 60% quartan infections of all the positive cases. Quartan comprised about one quarter of all the infections in the northern parts of Argentine. In some huts I even saw *all three forms* of malaria in different members of the same family who lived under the same conditions. Quite frequently we found *double infections*, in which almost constantly the estivo-autumnal parasite was associated with either tertian or quartan parasites. Only three times was tertian associated with quartan. Twice we found *all three kinds* of parasites in the *same* individual. Today I cannot go further into the epidemiological and statistical details of our investigations. The chief carrier of malaria in Argentine seems to be the widely distributed *Anopheles pseudopunctipennis*. It might also be worth mentioning that we found a large number of cases of splenomegaly in persons in whom at the time no parasites could be demonstrated, even with the thick-film method, which was used by us in all cases.

II. With our first examinations in the Province of Tucuman, we further found *microfilariæ* in the thick films of some cases examined for malaria. Careful investigations led to the discovery of actual foci of such *microfilariæ* infections, in some regions up to 48% of the cases examined. The occurrence of cases of *microfilariæ* in the Province of Tucuman was already known, since 1914–1916, through the investigations of Araoz and Biglieri, as well as those of Paterson. But only this year, through our own investigations and those made at the same time by Biglieri in the neighborhood of the town of Concepcion (Province of Tucuman) *could the surprisingly great distribution of microfilaria be established.* We found not only new foci in the Province of Tucuman, but also *new foci* in the provinces of Salta and Jujuy, and even up to Bolivia, and among Bolivians in these provinces especially. This led to the suspicion that the infection could be introduced from the Bolivian-Chaco, with the laborers coming into the northern provinces for the sugar harvest every year. These laborers are mostly Indians. Our investigations concerning the significance of this *microfilaria* infection are not yet finished, nor is the

mode of transmission nor the adult worm known. Nevertheless, I wished to report briefly about our findings, and especially to demonstrate photomicrographs of the *microfilariæ* which not rarely can be found in great numbers in the thick film. We have seen *more than 20 in one field* with the high-dry power of the microscope. In spite of such large numbers of *microfilaria* I could *not* make out a definite *clinical picture* of the disease. The symptoms sometimes given, such as headache, vertigo, and prostration, as well as anemia and edema of the eye lids, are symptoms which in countries with endemic malaria, ankylostomiasis and other similar diseases, do not justify the establishment of a new clinical entity.

The *microfilaria* can be found at any time of the day or night. Morphologically it was studied by Rosenbusch in 1916. He came to the conclusion that it corresponds to the *m. demarquayi.* On the other hand, Biglieri, in a morphological study just completed and published in "La Semana Medica," thinks that it is a new parasite, which he calls *M. tucumana.* Our own morphological studies are still in progress. It is interesting that *more than one half* of our 219 positive cases *were children* up to 15 years, and among these one child of 6 months. The two oldest infected individuals were 80 and 84 years old, respectively, without any definite clinical symptoms.

Also in the bird *Turdus leucomella* we found, in two instances, a *filaria* already described in Argentine by Biglieri and also in Brazil. These *microfilariæ* will be demonstrated after the lecture.

III. In addition, I desire to report briefly on the findings of two cases of *Schizotrypanum cruzi* occurring in Argentine: the first in the Province of Tucuman, and the second in the Province of Jujuy. After the publication of the important findings of Chagas in the State of Minas Geraes (Brazil), searches had been made for trypanosomes in Argentine, since the carrier, *Triatomas,* is numerous in these regions, and goitre and cretinism are found in many persons. But all searches up to the present were negative, including also the researches of the commission Kraus-Rosenbusch, sent from the Department of Health of Buenos Aires to study this question, in 1916. Kraus and Rosenbusch could only

establish that in certain regions the *triatomas only* were infected with trypanosomes, but *not man*. Nevertheless, I directed my attention, from the beginning, to our examinations towards this question, and I had the good fortune to find in the first few weeks a case with blood-infection of *Schizotrypanum cruzi*, by means of the thick-film method. The case occurred in a five-months-old child from the region of Monteros. The child was brought by the mother to the dispensary on April 14th, for examination. In the thick film I saw many trypanosomes, about 1 to every 5 fields, and in some fields 2. Also, in the 2nd and 3rd examinations, made several days later, trypanosomes were found. But in the *second* examination we found also *tertian* parasites, which in the 3rd examination had greatly increased. Therefore, we gave quinine. At the 4th examination, made 9 days after the first, and after the child had been taking quinine for several days, we found neither trypanosomes nor tertian parasites. The trypanosomes also remained absent during 2 months' observation in a clinic at Buenos Aires. Also, animal experiments with blood-inoculations from the child remained negative; perhaps because the injected mice died too early, from intercurrent diseases.

The *second case* was in a child about 8 years old. The blood from this child was taken May 10th, in the school at Paulina (Ledesma). At the examination of the blood, made 18 days later in Buenos Aires, my collaborator Zuccarini found only *one* trypanosome in the thick film. Following a telegraphic request, Dr. Zieschank (Ledesma) sent other thick-film preparations taken May 30th. Also in these films we found only one trypanosome in every drop. All the later examinations of this case, which was *not* complicated with malaria, were negative. But it was possible to *infect a mouse* with 1c.c. of blood from this case taken on the 9th of June, when repeated blood examinations had been negative. Twenty days after the blood injection the mouse had the first trypanosomes. This experiment showed that *even at time of apparently negative blood-findings it is possible to demonstrate* trypanosome infections when sufficient blood is taken for animal infection, and when the animal is observed for a sufficiently long period of time.

Perhaps by this method of animal experiment a higher percentage of trypanosome infections can be established.

In this connection I wish to mention a *successful guinea-pig infection by bites from four triatoma infestans* which were taken from the house of the *first* case. The triatoma had bitten the young guinea pigs on May 31st, and on June 28th we found the first trypanosomes in the blood of a guinea pig. Also, the examination of the intestinal contents of one of these *triatomæ* showed the well-known typical flagellates. This observation was made just before my departure for this Conference, and the investigations are to be carried on.

Concerning the *pathogenicity* of the trypanosome infections observed, we cannot yet state anything definite. The first child showed symptoms of anemia, prostration, slight edema of the eyelids and hands, fever, an enlarged spleen and enlarged cervical lymphnodes. So that at first glance I had the impression that it was a case of the so-called acute Chagas disease. But the later demonstration of tertian parasites in the same child does not permit us to attribute *all the* described symptoms to the trypanosome infection.

In the second case, at the examination made in the school, we noted a slight enlargement of the spleen and thyroid. The history taken later showed that the child had never been sick up to that time. But the parents said that about four weeks previously she had been bitten on the face by the "vinchucas" or *triatoma* (*barbeiros*). This child also had slight enlargement of the cervical lymphnodes.

In over 7,000 blood examinations made in the subtropical countries of Argentine we were able, therefore, to find *only two cases of trypanosomiasis* with the *thick-film* method, and only with *this* method, in spite of the fact that we worked in regions where cretinism and goitre were common. For instance, in some portions of the Province of Salta we saw goitre in more than 60% of the cases examined. Our two trypanosomiasis cases occurred about on the same geographical latitude as those cases described in Minas Geraes in Brazil, by Chagas.

Of *other diseases in Argentine* I cannot go into detail, but want to mention briefly that *cutaneous Leishmaniasis*

sometimes occurs, and also that we saw some cases of *espundia* introduced from Bolivia.

Mal de caderas occurs in the Gran Chaco in large numbers. We have already started prophylactic treatment with "Bayer 205." *Typhus* (spotted fever) occurs in the higher parts of the province of Salta. *Syphilis* and other venereal diseases, as well as *ankylostomiasis, tuberculosis and alcoholism*, are widespread. Cases of *yaws* were not seen, but some cases of *granuloma venereum* were seen. *Lepra* and *Plague* occur in some regions, especially in the Chaco. *Typhoid* and *paratyphoid infections* are not rare, and *amebic dysentery* is also found frequently in some regions.

DEMONSTRATION OF PHOTOMICROGRAPHS

Summary.— (1) The northern provinces of Argentine are markedly infested with malaria. Our investigations showed that estivo-autumnal and quartan forms are more numerous than was previously assumed. Estivo-autumnal could be found in a high percentage, up to an altitude of 1,200 meters.

(2) *Microfilaria* infection is also more extensively distributed than has been known to be the case up to the present. We found new foci — not only in the Province of Tucuman, but also in the provinces of Salta and Jujuy — present in 48% of the examined population. The adult worm and the carrier could not be established. According to Rosenbusch, the microfilaria of Argentine is most closely related to *M. demarquayi*.

(3) In northern Argentine we could find *Schizotrypanum cruzi* in two children, with the thick-film method. Also, animal infection was successful by the bite of *triatoma* obtained from the hut of the first case, and by the injection of blood from the second one. Concerning pathogenicity of these trypanosome infections, occurring apparently so rarely in Argentine, further investigations are necessary.

DISCUSSION

Dr. Charles Bass (*Opening the Discussion*).— I wish to express deep interest in this splendid report, especially the part referring to malaria. I think that all of us must be impressed with the

fact that this, and much other evidence obtained from similar surveys, indicates that malaria is a disease of vast importance throughout the world. Here we have, in a single examination, over 30% of the population found infected with malaria. Experience shows that the findings on a first survey do not represent more than perhaps about 50% of the total of all infected. Therefore, in the people among whom Professor Mühlens was working in the Argentine, perhaps at least 75% have malaria during the year, and no doubt suffer more or less from it.

I wish to ask Professor Mühlens what his opinion is, as to the significance of the splenomegaly in cases in which he does not find malaria parasites. Does he believe that this is the result of previous malaria, or does he think it is due to some other disease? My impression is that such cases improve and the spleen comes down, on malaria treatment, but some of them do not yield in the same way that other large spleens, accompanied by a large number of parasites, do. I hope we may hear further remarks by Professor Mühlens in regard to this subject.

Dr. H. J. Nichols.— I have nothing to say except to express my great interest in this paper which, as we say in slang phrase, is "right off the fire." It is evident that there are a great many infections in this country. The use of the thick-film method apparently should be extended, because there are a great many of us who use it only occasionally. The appearance of these new cases of trypanosomiasis suggests probably that it may be as widespread in this country as in Brazil, and the suggestion that *filaria* is imported from Bolivia is interesting.

Dr. Hideyo Noguchi.— Perhaps it may be of some interest to record here an instance of human trypanosomiasis in northern Peru, detected by means of culture.

In the summer of 1920, cultures were made by Drs. Kligler and Caballero from 5 cases of yellow fever that occurred at Morropon, a town near the foot of the Andean range, in northern Peru. In one of the culture tubes inoculated with the blood of one of the patients, I was able to detect the growth of a flagellate, undoubtedly the cultural form of a trypanosome, simultaneously with *Leptospira icteroides*. For this medium (so-called *Leptospira medium*) the flagellate remained viable for many weeks, at room temperature.

From this observation it seems that in a survey like that undertaken by Professor Mühlens, the use of such media might facilitate the finding of the infection in a higher percentage of cases. This is merely a suggestion.

I offer my congratulations to Professor Mühlens on his splendid contribution.

Dr. Friedrich Fülleborn.— It may be remarked that *Schizotrypanum cruzi* is found by Dr. Segovia, in Salvador, in human blood and that the parasite may occur also in other parts of Central America—for example, in Guatemala.

Dr. Henry Rose Carter.— Some notes, to which I have already alluded, have been made during recent years by LePrince, Griffiths, and myself on minor variations in the biology of certain Anopheles in different regions, and Dr. Mühlens has here developed a regional variation of a mosquito's relation to the malarial parasite which is most interesting. Darling found *Anopheles pseudopunctipennis* quite difficult to infect with malaria, in Panama. My recollection is — I am not positive of the proportion, however — that he found about seven times as many *albimanus* showed infection as did *pseudopunctipennis*, under the same conditions of exposure. Herms, after a malaria and mosquito survey in California, regarded *pseudopunctipennis* as of minor importance as a vector in nature, in that state, and I think that that opinion is held of it in those parts of the United States in which it occurs — I have not seen it east of the Mississippi River. Yet Dr. Mühlens reports it to be a very efficient vector of malaria in parts of Argentina: a thing worth noting and, taken with Darling's and Herm's observations, *well* worth noting.

As to the distribution of American Trypanosomiasis (Chagas Disease) I would say that I was shown the Tritoma, the vector of this disease, commonly known as "*o barbiero*" ("the barber") and was told of cases when I was at Fortaleza in the State of Ceara, almost the extreme north-eastern point of Brazil. And this showing, by Dr. Mühlens, of its occurrence in the State of Tucuman, in Argentina, is close to (and beyond) the southwest end of Brazil. This infection then would seem to extend entirely across Brazil, from the north-east to the south-west. I was also told, by Dr. Chagas last year, that it was found in the extreme north of Brazil, close to the Venezuelan border.

This, as is well known to you, is one of the infections of man of which the causative organism has reservoir hosts — like the African trypanosome in relation to some of the big game of that country, and the spotted fever of the Rocky Mountains of the United States. One, or possibly *the*, principal reservoir host for this trypanosome is the armadillo, which, it is claimed, carries the parasite and is infective to its insect vector indefinitely. The insect vector is nearly as large, although not as thick, as one's thumb — hence a fine meshed screen would not be needed to exclude it.

Dr. P. Mühlens (*Closing the Discussion of his Own Paper*).— With my best thanks for the great interest which you showed in

listening to, and discussing my paper, I will answer the questions asked by Dr. Bass and Dr. Noguchi.

I think that the splenomegaly which we found in so many cases without parasites is mostly due to past or persistent latent malarial infections; notwithstanding, there is no doubt that many cases of splenomegaly can be produced by other diseases, especially by syphilis, which plays an important rôle in the northern parts of Argentine.

The communication of Dr. Noguchi about the occasional finding of trypanosomes in Peru, by cultures made for yellow-fever studies, is very interesting. We also in Argentina have intended to make blood-cultures, as well as animal infections, and I am sure that we shall find more cases of human trypanosome infections in this way.

SOME ASPECTS OF TROPICAL MEDICAL WORK

A. E. Horn, M.D.

The problems in preventive and curative medicine which are present in various parts of the Tropics, are somewhat of the nature of a kaleidoscope. Some of the elements may be missing from certain areas, but the complex retains the greater number arranged in different patterns so that one or another feature attains a predominance, and more urgently demands attention than the remainder. Not only is this the case for different places, but it is equally so for different periods, — a turn of the kaleidoscope converting the unobtrusive parts of one view into the insistent features of another, when a smouldering endemic disease lights up into epidemic outbreak.

It is within our province, who are concerned with these factors composing the kaleidoscope of tropical diseases, to study and deal with each aspect as it presents itself — in time or place — and to so regulate our exertions as to meet the pressing needs of the moment, while a steady effort is maintained against the temporarily less obvious components.

Thus, in the end, we may hope to eliminate the purple patches, and reduce our field of action to a drab monotone — a consummation devoutly to be wished, but hardly likely to be attained in the near future.

Malaria is ever present in the background, with rare exceptions, such as Fiji, where for some imperfectly understood reason, the malaria-bearing Anopheles is absent — a blessed state of affairs which is shared by the island of Rodriguez, about 350 miles from Mauritius, in the Indian Ocean. But whereas Rodriguez receives protection against steamer-borne mosquitoes, by its coral reefs which keep the ocean-going steamers at a safe distance of 5 or 6 miles from its shores, there appears an appreciable risk of deep-sea steamers' bringing the fateful Anopheles from other lands to Fiji where steamers moor alongside at Suva.

Should the malaria-bearing mosquito unfortunately effect a lodgment in Fiji — where cases of malarial infection are

common enough in individuals of the imported Indian Coolie class — it is difficult, in our present state of knowledge, to say why epidemic malaria should not flare up with devastating results among the aboriginal population, as yet innocent of this disease. Thus might be repeated, by a turn of the kaleidoscope, the calamitous state of affairs which arose during the middle 60's of last century, in Mauritius, when, apparently following the introduction of malaria mosquitoes, over 30,000 deaths occurred from fever alone in one year.

Perhaps few subjects in tropical sanitation have received such close study, of late years, as the enormously important one of malaria-prevention. Leaving aside the vexed question of prophylactic quinine in a malarious neighbourhood, and the obvious necessity of protecting malarial patients from mosquito bites, we may glance briefly at the broader aspects of prevention, in the mass. These resolve themselves, in one way or another, into attacks upon the existence of Anopheline mosquitoes which are known or suspected carriers of the malaria parasites, and it is needless to dilate on the necessity for attacking them in the most vulnerable link of their life history; *viz.*, in their pre-imaginal state, which is passed in water. Naturally, where there is no water we shall get no mosquito-breeding, but since water cannot be eliminated entirely from the order of things, we endeavour to control the facilities for breeding, by drainage, oiling, fish-stocking, etc. — more or less expensive methods, which may unfortunately prove occasionally disappointing in their results.

Long and sad experience has proved that we shall not achieve the best results by any ill-considered or indiscriminate action. What is sauce for the goose is not necessarily sauce for the gander, when dealing with Anophelines and their breeding places. Much money has been spent and labour expended in the past, with the idea that conditions which have proved unfavourable to the development of one species of Anopheles must of necessity be unfavourable to all. On this theory, in the past, in Malaya the mountain streams which are so frequent on the rubber estates of that well-watered country, were cleared of the shrubs and vegetation which shaded the ravines in which they flow, so that, as it was hoped and expected, the advent of additional sun-

light and air would render the water unsuitable for *A. umbrosus*, the prevalent malaria mosquito. The result, however, was found to be that the cleared streams attracted another and more active malaria-carrying species, *A. maculatus*, and the last state of those streams became worse than the first.

To avoid such mistakes must be our endeavour and, next to careful identification of malaria-bearing mosquitoes, a precise study of their habits is of the greatest importance — so we may get to understand why, for instance, it is that *A. maculatus* is of the greatest importance as a malaria-carrier in Malaya, and of comparatively little effect in Sumatra, while *A. ludlowi* is found extensively inland, and is the main bearer of malaria in Java and Sumatra but is of comparatively little importance in Malaya, where it is largely confined to the sea coast; why certain rice fields in Malaya are intensely malarial, while others apparently under precisely similar conditions do not give rise to malaria. Similar problems are to be met in most parts of the Tropics, as, for example, the limited range of *A. funestus* in Mauritius, which was found by Macgregor to be confined below an altitude of 500 feet, whereas in Africa its range is up to over 5,000 feet from sea level.

Probably the solution of some of those problems lies in consideration of the food stuffs of the larvae; of possibly as yet unrecognized enemies and parasites; or, in some cases as Watson suggests, in the nature and amount of pollution of the water.

In all circumstances, however, the value of sub-soil drainage must be recognized for marshy areas which are not amenable to contour draining. This is only too frequently a costly undertaking, necessitating the services of an engineering staff and expensive piping or drains; but still, I have known some such areas effectively dealt with by the medical officer of health laying down, instead of pipes or tiles, lines of perforated cigarette and milk tins, placed end to end, to form an efficient sub-soil conduit. Again, good results were obtained by Brooke in the quarantine island of St. Johns, at Singapore, by utilising old waste sheets of corrugated iron, which he bent into arches, and buried end to end, with small intervening spaces so that the swamp water drained

under the arches and was conducted to a safe outlet.

These, I grant you, are but temporary expedients, and not worthy of consideration where ample funds are at command, but they are none the less worth remembering when in a tight corner with no spare money to play around with since, when intelligently carried out, they have the advantage of disposing of useless rubbish — which may itself be the means of mosquito breeding — and so these expedients may produce good out of evil.

In regard to the curative treatment of malaria we cannot yet be said to have reached finality. There are some, amongst whom I confess I include myself, who regard a maximum amount of 30 grains of a quinine salt in solution, taken by mouth, during 24 hours, as curative of most attacks of malarial fever. Let me add the proviso, however, that a preliminary or accompanying early saline purge is almost a *sine qua non*, while it is obvious that if an inflamed and irritable stomach cannot retain the drug, another method must be tried. On the other hand, we find it stated by some writers that "doses from 30 to 130 grains a day were given over a week or more with literally no apparent effect." There is, I think, little doubt that in cases where such enormous doses as these "were given," the same amount was by no means "being taken" by the patient, who either discreetly dodged his medicine, or failed to absorb it, or retain it on an irritated stomach.

Fletcher — whose work on the treatment of malaria as carefully supervised by him in the Medical Research Institute in the Federated Malay States has shown the extreme importance of making certain that a patient is really taking the quinine which is prescribed for him — found in 1918 that a standard dosing by mouth of 20 grains a day was sufficient to cure the many "quinine-resistant" cases of malaria, amongst British soldiers invalided to England from various theatres of war. But he made very sure, by personal attention, that his patients were really swallowing their medicine!

Alternative methods of treatment by quinine are those of the intravenous, the intramuscular, and the rectal injection of a soluble salt. Of the former there is little to be said, except that its necessity must be admitted for the gravest cases where quinine cannot be taken by the mouth. It

should, however, be confined to such cases. Of the intramuscular method much has been said on each side, as to its value. We have all of us, no doubt, employed it to a considerable extent, and no doubt in some cases have been convinced of its good effects, but I am equally sure that all of us have heard of cases, even if we have not met them in our own experience, where abscess formation and necrosis have followed at the site of injection. And such efforts have sometimes resulted in the permanent maiming of a patient. This is a serious matter which must make us pause and consider whether we are indeed justified in submitting our patients to such a risk, except under the direst necessity.

Fletcher, whose work I have referred to above, tried the experiment of treating 22 malarial patients by the intramuscular injection of 20 grains of the bihydrochloride, dissolved in 44 minims of salt solution, half the dose being given in each buttock. He also treated a similar group of patients by giving the same dose by mouth, and comparison between the two groups was made by examination of the urine for the presence of quinine, as an index of its absorption into the system and subsequent excretion. As a result of this trial of methods, he found that, in the intramuscular group, quinine first appeared in the urine after 20 minutes; the longest time for it to appear was 200 minutes and the average time between the injection of the quinine and its appearance in the urine, was close on 60 minutes. In the group to which the quinine was given by the mouth, the drug first appeared in the urine in less than 15 minutes; in no case did it take longer than an hour to appear, and the average time between its administration and detection in the urine was 31 minutes.

That is to say, judging by this criterion, quinine by mouth is absorbed into the system in about half the time in which it is absorbed from an intramuscular injection. In both sets of cases, the quinine could no longer be detected in the urine after 26 hours from the administration, so that no advantage in the way of "storing" quinine in the system was obtained by the use of intramuscular injection.

I think you will agree with me that these results are very suggestive and indicate that treatment by intramuscular injection should not be a routine measure for patients who can swallow and retain their quinine solution.

The last method to be considered is the rectal injection of quinine, which has long been a recognised, if not esteemed, mode of treatment. Here again, Fletcher has carried out careful experiments giving by slow rectal injection about 30 grains of quinine bihydrochloride in water or normal salt solution to different patients, the amount of solution varying from 2 fluid ounces to 15 fluid ounces in different cases, and sometimes being combined with starch and opium. He describes the effects as "most shocking and striking." Some of his patients suffered from severe collapse within 15 minutes of the injection, with colic and the passage of blood and mucus, which continued for from 24 to 72 hours after. No quinine could be detected in the urine.

These results were considered of so great importance that the Colonial Advisory Medical and Sanitary Committee of the Colonial Office requested Dr. Fletcher, in 1923, to continue his experiments and note the effect of such administration on animals. This has since been done with ample confirmation of his previous findings. Guinea pigs voided the injection almost immediately after it was given, pain being apparently suffered. In human beings the carefully noted effects are very striking. In 2 different sets of experiments the injections consisted respectively of 20 grains of quinine bihydrochloride in 4 oz. of salt solution, and the same amount in 8 oz. of salt solution. They were given twice daily, and a money prize was given to the patient who retained his injection the longest.

Of the group with the stronger injections, no one could retain the injection longer than 35 minutes and the average time was 13 minutes; out of 132 injections, in 96 instances quinine could not be detected in the urine. With the weaker solution, 25 out of 32 injections were returned in less than 20 minutes, and only 3 injections were permanently retained; quinine was found in the urine after less than 60% of the injections, and was often no more than a trace. In subsequent trials of these cases, by giving them 10 grains of the same salt by mouth, quinine appeared abundantly in the urine.

The effect on the mucous membrane of the rectum was marked, mucus and large shreds of membrane being passed in stools subsequent to the injections, with pain and tenes-

mus. As a curative agent the method was found ineffective, parasites being found in the blood in several cases after a week of injections, when quinine by mouth was successfully substituted.

In the light of this valuable work of Fletcher's, it appears that our former position as regards this mode of treatment of malaria demands careful reconsideration.

Of other mosquito-borne diseases which form elements of our kaleidoscope, we must include yellow fever, filariasis, and dengue; and of this group it is unfortunately the case that our opposing efforts are almost limited to the preventive side, and we possess no drugs or medicaments which we can claim as specifics in treatment. But let us be thankful for small mercies and recognise that since the conveyance of these diseases is dependent on domesticated or semi-domesticated mosquitoes, we are in a powerful position to deal with them on the preventive side of our profession.

Generally speaking, the life and habitat of these Culicine mosquitoes are in proximity to mankind, and it is very largely the case that it is by the actions and defaults of mankind that they are able to live and flourish — to our own undoing. For it is in the promiscuous puddles and open collections of water which the uneducated man tolerates in his neighborhood, that the origin of many of his evils lies, and it is for his instruction, and to help deliver him from the evil consequences of his actions and reactions, that we are compelled to maintain large and expensive sanitary organisations.

Obviously, some of the most important work of a Health Officer is the prevention of mosquito-breeding in towns and villages which are susceptible to the diseases I have named, — and the success attained by him and his sanitary staff will depend very much on the enthusiasm and constancy with which he carries out his duties. Tact and energy are essential qualifications, and an adaptable mind which recognises that there are other ways of killing a dog besides choking it with butter. Methods which have been employed to instruct the people of one country or tribe, with marked success, cannot always be so usefully employed with another, but, bearing in mind the main objects of his work, the Health Officer will endeavor to accomplish his end with the minimum friction and offence to local needs or prejudices.

Drinking water is essential for all people, even in countries which have not yet discovered the blessings of prohibition, and the provision of a pipe-borne water supply is a luxury which is out of the question for thousands of towns and villages throughout the British Colonies. In Malaya more or less satisfactory water is almost always available in the "kampongs," or native villages, and little or no private storing is required. In many parts of West and East Africa, on the other hand, the procuring of drinking-water forms one of the main problems of life. — It may be carried in pots and calabashes for miles, from a stream, river, or shallow well, and stored with the utmost concern for consumption during the dry season, but the fact that such stored water is freely accessible to mosquitoes, and may contain larvae by the hundreds, is a matter of supreme indifference to the native.

Yet it would be iniquitous for an energetic Health Officer or Sanitary Inspector to condemn the storing of water under these conditions, or to oil the supply contained in the domestic pots, as it is required for drinking and cooking. He can do little more than insist that they shall be kept constantly covered with a cloth.

Shallow wells, perhaps 6 to 10 feet deep, form a general source of water supply in many African villages. As they are usually freely open to the surface, they are equally common sources of mosquito-breeding. Oiling is undesirable, but occasionally fish-stocking can be effected, and I have known cases where one or perhaps two fish — grown to 8 or 10 inches in length — have for years past kept such a well free from mosquito larvae. On the whole though, the only practical solution is to reduce such wells in a village to the minimum number, close in the opening with a parapet raised above the level of the surface so as to avoid contamination, and draw up the water by a windlass and bucket through a closable trap-door, at certain fixed times. It must be remembered that expensive remedies — such as helical chains — are generally out of the question, while pumps appear to be an invention of the devil from the constancy with which they get and remain out of order.

Rain-water caught from the roof of a dwelling, and stored in tanks or casks, is one of the best drinking supplies when

no pipe-borne supply is available. But it is just as dangerous a source of mosquito-breeding as the others, unless it is properly protected against mosquitoes.

This is usually done by fixing metal mosquito gauze over the inlet of the tank or cask, immediately under the down pipe which conducts the water from the roof; and the method works perfectly well so long as this gauze remains intact. But the life of the gauze is short; it rots away and holes develop in it through which mosquitoes can get freely to the water. It wants constant watching, and will frequently let down the unsuspecting Health Officer, who finds to his disgust that what he considered a protected water-supply is supplying him with more Culicine mosquitoes than he has immediate use for.

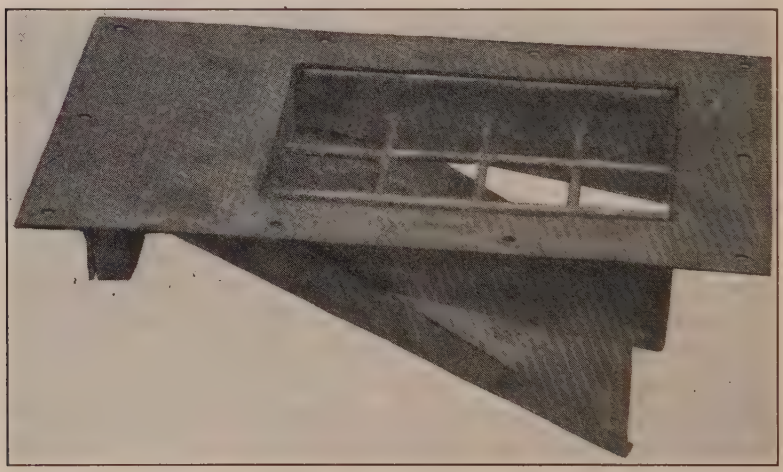


FIG. NO. 1.

With the object of obviating this source of mosquitoes, I devised a small contrivance which I found to work admirably under all conditions of the rainy season in the Gambia (West Africa), and I venture to put it before you now. It entirely replaces the gauze protection of a tank, and acts automatically without need for adjustment, accommodating itself equally to the rush of water from a tornado or the slightest drizzle of a light shower.

As you will see, the apparatus is, briefly, a metal plate with an oblong opening in the centre, surrounded by a flange on

the lower side. Against this flange, and in close contact with it when at rest, impinges a trap-door with a counter-balancing weight to secure apposition. The whole is rendered rust-proof by galvanizing *en bloc*, and is screwed to the top of the water tank or cask so that the opening is immediately under the down-pipe conveying the water from the roof-gutters. There are no springs to get out of order.

With the fall of water on it the trap-door opens to an extent corresponding with the pressure, and with the cessation of the fall of water it closes and is kept closed by the counter-balance. While mosquito larvae from a defective roof-gutter may wash into the tank, it was found in practice that no mosquitoes could escape from it, either when the inlet was at rest or when water was passing through it. A few cross wires on the top prevent the unwarranted intrusion of lizards, birds, etc. into the tank. It is of sufficiently rigid construction to prevent distortion of its parts.

This device is now being made by Messrs. Frederick Braby and Company, Limited, Galvanized Iron and Tank Manufacturers, 110 Cannon Street, London, E.C. 4., at the following charges, which in each case include packing and delivery f.o.b. London.

One only	14*s.* 0*d.*
One dozen	8*s.* 0*d.* each
One gross	5*s.* 0*d.* each

You will notice that in considering these possibilities of Culicine mosquitoes and certain of their breeding places, I have referred in the main to conditions which are bound up with the more primitive races of mankind who are but lightly touched by civilisation. Such people exist in millions scattered through the hinterland of West Africa and East Africa. Their diseases and complaints are year by year becoming increasingly known to us, but full knowledge is not yet with us, nor will it be accomplished without much patient thought and investigation.

There are many problems which urgently demand attention, and not the least is the question of yellow fever in West Africa. It admittedly exists there, but its recognition depends on its clinical and post-mortem manifestations, and its relation to the prevalence of the Stegomyia. So far, the

Leptospira icteroides has not been found in connection with any case. Experiments were carried out in Lagos, Nigeria, in 1920, when I was working the subject in connection with the Yellow Fever Commission to West Africa, under the auspices of the International Health Board, to ascertain the effect of Pfeiffer reactions, agglutination and protection experiments with strains of *Leptospira* from the yellow fever centres in America and serums from local cases of what were apparently yellow fever recoveries. They all either failed or were too irregular to be accepted as evidence of identity, and further investigation is required.

In the meantime, one can only express agreement with Noguchi that "for complete eradication of yellow fever the anti-Stegomyia campaign is the ultimate measure to be relied upon."

DISCUSSION

Sir James K. Fowler (Opening the Discussion). — I am sure the Conference will recognize the very practical character of the paper, and the great value of the contribution which Dr. Horn has just made to our transactions.

Concerning the question of the disappearance of malaria, I wish to mention an experience hitherto unpublished. In 1878, at Addenbrooke's Hospital, Cambridge, I saw several cases of malaria patients; come to the hospital from every village in the surrounding country, once the Fen country, the last well-recognized home of malaria in England. Malaria had not died out, withstanding the drainage of the Fens. On the return of soldiers from the World War, the number of infected persons in England became quite considerable, and again the Fen district produced cases. I think malaria had never been absolutely non-existent in that part of England.

I doubt whether a disease known in historic times has ever been absolutely "eradicated" or removed from the surface of the earth. It may be destroyed locally, as we all know, but has a single disease known to us through the writings of the ancients ever been "eradicated" — pulled up by the roots, not a shred of its vines left — and all this due to the action of man? If not, it is not advisable that we should speak of a disease as having been "eradicated," when all that has been done is to destroy a local center.

Dr. Hideyo Noguchi. — I was greatly interested to listen to the valuable discussions of Dr. Horn on various health problems in the Tropics. Among others, his reference to the negative findings of

L. icteroides on the West Coast of Africa particularly interested me.

I happen to possess a copy of the complete report of that Commission (1920), and by going over details I have found that they had not found a single acute case of yellow fever during their entire sojourn on the West Coast of Africa. There was a suspected case of yellow fever in a native, but before Dr. Stokes could reach the patient the latter disappeared. I remember also the absence of a Pfeiffer reaction in the serums of a few persons who were supposed to have had yellow fever some time past. Of course, these results were not regarded as evidence of the absence of *L. icteroides*.

I wonder whether the expedition of 1920, with which Dr. Horn was associated, was the same as that which I have referred to here. If not, I should very much like to know how many early cases of yellow fever were studied by Dr. Horn and his colleagues with a view to isolating *L. icteroides*. Was any animal transmission attempted? It may be stated that a direct microscopical detection of this organism is extremely difficult, even in the infective stage of yellow fever, and positive transmission can be hoped for only when young guinea pigs are being used. I should be very much indebted to Dr. Horn if he would give this Conference his personal experiences in this phase of research.

Dr. P. Mühlens. — Many experiences during and after the World War demonstrated the fact that malaria can be introduced into regions where Anopheles mosquitoes exist. So in North Germany, in the country of Emden, where the *Anopheles maculipennis* is very numerous, in the last 2 years of the War we had about 4,000 cases of tertian infections; also, in Berlin, in the environs of which Anopheles are widespread, in the last years since the War about 50 cases of estivo-autumnal infections were found. In Dalmatia (Serbia), in localities previously free from estivo-autumnal infections, these infections were introduced by carriers of parasites who returned from the War.

Such reappearances of malaria can be prevented only by the extermination of the transmitting Anopheles mosquito in the same classic manner as that adopted by General Gorgas and his collaborators in the Panama Canal Zone.

Dr. J. A. LePrince. — I should like to make a few remarks regarding Anopheles-control, and desire to call attention to the question of Anopheles production in seepage outcrops.

We have many instances in the Tropics in which mosquito breeding places are of intermittent character. It is often the unknown place, from which the Anopheles come. In Ancon, we had one seepage outcrop which appeared for 4 weeks, and had been present only once before in 10 years. We expect seepage to start in

the wet season. In some instances at Panama our seepage started at the end of the wet season, and continued during the dry season.

Frequently, in the case of some of our Tropical-American Anopheles, we look about our houses and say we have very few Anopheles. I have seen several instances in which a horse was taken along with the observers, and so many Anopheles were observed on the horse that it took 3 people to catch all that arrived, even in a locality where it was said that there were none of these mosquitoes.

In regard to the question of resting places of Anopheles, and of light and darkness, — many of the Anopheles will not come where we have a certain high candle-power of light. Apparently intense light is repellent.

As to Anopheles in houses and about houses, we expect to find them in the dark places, but not all species rest in places which are too dark, and frequently in places that are very dark we get no Anopheles at all.

Concerning the question of Anopheles-control by "swatting," sometimes we have had a high malaria rate in camps where they had fairly good screens, and 40 times as much malaria where there was not daily destruction of mosquitoes as in houses where daily catching or swatting was the method used.

With regard to screening, it was mentioned that screens will decay. The Monel metal used for making screening lasts several times longer than copper bronze. When the iron in copper-bronze screen exceeds ½ of 1% of the alloy, the more the excess of iron the shorter the life of the screen.

Dr. Charles C. Bass. — I was interested particularly in that part of Dr. Horn's paper which dealt with the treatment of malaria. There seems to be no hope that we may at any early date arrive at a definite agreement as to methods of treating malaria. There is also considerable difference of opinion as to the demand for administration of quinine by intra-muscular injection, and as to the relative value of this method as compared with oral administration. Those who are open to conviction and who wish to arrive at the proper conclusion may be the better able to do so if they keep in mind certain fundamental facts relating to the matter, which I believe all agree upon.

The purpose of giving quinine for malaria is either to relieve existing clinical symptoms, or to destroy the malaria parasites in the patient. To know the method of administration by which either or both of these purposes can be best served, is naturally desired by all of us.

Clinical symptoms due to malaria disappear promptly when

quinine is given by mouth. I have not personally been able to observe any exceptions. This has been the experience also of many other observers. On the other hand, there are those who believe they have seen malarial fever continue for many days — in spite of quinine administered orally — but stop almost at once from an intramuscular injection of only 1 or 2 doses. Such cases are often clinical diagnoses, not confirmed by finding parasites in the blood and by further thorough examination by which other disease is ruled out. Barring such questionable cases, quinine administered orally is always as effective in relieving the clinical symptoms, as the same amount administered intramuscularly, — perhaps the oral method is more effective.

The other purpose of giving quinine by either route is to destroy the malaria parasites in the patient. This is the effect, upon the malaria parasites, of quinine that reaches the blood stream. Every published scientific research on this subject that has come to my notice, indicates that quinine reaches the blood stream, and through it the urine, more promptly and in larger quantity when administered by mouth, than when administered intramuscularly. Not only is this true, but the malaria parasites disappear from the blood more rapidly. Therefore, there certainly is no advantage in this regard in giving the quinine intramuscularly. Enthusiastic advocates of this method may claim that it causes parasites to disappear from the organs and tissues of the body more rapidly or more certainly. I submit that such claim is based upon imagination only.

I must disagree with the idea that has been advanced, that malaria patients should be individualized with regard to dosage and duration of treatment. It is a fact that the clinical symptoms will be relieved by a smaller amount of quinine in a given case than in another, — but it is also a fact that there is no clinical or laboratory examination by which we can determine which case will require the larger or the smaller amount. It is necessary, therefore, to give an amount that will relieve the symptoms in *all* cases; 30 grains daily will do this in all cases within 3 or 4 days, but less may sometimes fail.

Different individuals have to take quinine for very different lengths of time, to cure the infection and prevent relapse; but here again we are not able, by any clinical or laboratory test, to determine who will require a longer or a shorter period of treatment. We must, therefore, administer the quinine for long enough in *each* case to cure the infection in practically *all* cases. This will mean about 8 weeks. Failure will be in proportion to the extent to which this period is shortened. We cannot determine by any examina-

tion when a patient is cured of his infection. If we could, we might be able to advise certain individuals to discontinue quinine earlier than others. The fact that we cannot, demands, as I have said, that *all* patients should be given quinine treatment *of such duration as to guarantee cure of the infection in practically all cases.*

Although we do not now entirely agree on the doses of quinine necessary, or the need and usefulness of intramuscular injections, I believe if the facts just mentioned are recalled from time to time, there will be a more general use of the treatment which I believe more nearly meets the needs, *viz.*, the *standard treatment*, consisting of 30 grains quinine sulphate, by mouth, daily, for 3 or 4 days to relieve the clinical symptoms, followed by 10 grains daily for 8 weeks to cure the infection.

Dr. Charles A. Kofoid. — We should determine the time in the life cycle of the parasite at which treatment for malaria should be given. The period of greatest susceptibility of any organism is in its early stage of development, following fertilization of the egg. It is possible that in the case of the malaria parasite this period recurs at sporulation when the merozoites are young. It has been found that in the case of rats and mice the death rate of the embryos in the uterus is highest in the earliest stage. In frogs' eggs, the highest death rate follows immediately after fertilization. The regulation of the weight of dosage in accordance with the susceptible period of the parasite, is suggested by this fact of the greater susceptibility of the young individual.

Sir Leonard Rogers. — What impressed me most the other day, was that it is not possible to lay down any general rule to deal with malaria in all parts of the world. In India, although I am in favor of intravenous injections in the most serious cases, I am convinced by Dr. Macphail and Dr. James, that the intramuscular injection is of great value in special circumstances, but it is necessary that you must have absolute sterility.

I spoke, before, of my method of injecting bi-hydrochloride of cinchonine instead of quinine intramuscularly; this, I think, combines the advantages of the simplicity and safety of that mode of administration, with the rapidity of action of intravenous injections, owing to the cinchonine salt being absorbed from the muscles far more rapidly than quinine, as shown by the signs of cinchonism following its injection within about half an hour. I hope this will be tested further.

The lesson to be derived from this valuable discussion is, that we should learn from the experience of others, and not limit ourselves to one routine method of treatment of malaria.

Dr. William M. James. — It is not my intention to discuss any

further the treatment of malaria. That has been most thoroughly gone into, and I do not wish to take up any more time on the subject. But the remarks of the preceding speakers, with the others that we have listened to from time to time during the Conference, would most certainly seem to lead an impartial observer to believe that there is a marked disagreement among those present as to the treatment of malaria.

But I do not think that this is true, and I shall endeavor to explain my reasons for this statement. I believe we are all in agreement that malaria should be treated with plenty of quinine. There is, of course, a difference of opinion as to how this quinine should be given, to obtain the best results. But I do not believe that the method of administration matters very greatly. For instance, although I prefer to give quinine in liquid form whenever I can, I am convinced that very good results have been obtained by administering it in powders and in capsules. If it is given in a form insoluble in the stomach and intestines — as, for example, in the compressed pills of commerce — it will often pass through the bowel unchanged, and so fail to give results.

Not only is the treatment of each case of malaria an individual problem, but the conditions involving the treatment of large numbers of cases under varying circumstances also present problems which cannot be solved by any hard-and-fast rule, except the good old rule to get enough quinine, by some method, into the patient to stop the fever.

There are 2 factors involved; the first is to save life in severe cases, and the second is how to restore the patient to health and to efficiency. Methods that will accomplish these ends under some circumstances, will fail under others. For instance, I agree with Dr. Bass as to the desirability of impressing upon the medical student a standard method of treatment of malaria, but I am sure that Dr. Bass himself will not teach that this method is applicable in all cases and under all circumstances, however good the results in certain cases and under certain conditions.

This is the point that we must keep in mind. I am sure we are all in agreement that when the physician is called to treat a case of malignant malaria in which there is great prostration and almost continuous vomiting, quinine should not be given by mouth. And I am also sure that in most cases in which quinine can be given by mouth, and retained, none of us would use hypodermic or intravenous injection of quinine, except in those rare instances in which with rather mild symptoms there is a very heavy infection in the peripheral blood, which must be attacked as directly and as quickly as possible.

In very urgent cases, the choice between a hypodermic and an intravenous injection lies in the judgment and the experience of the physician, and no amount of discussion can alter this. It would seem, in such cases, rational to give intravenous injections. But quinine is a powerful cardiac depressant, and when given intravenously, even in small doses, is sometimes followed by alarming consequences. On the other hand, small doses will not suffice in urgent cases.

If we take all of these facts into consideration, I do not believe that there is any great difference of opinion among us, and that is the principal point which I wish to make clear to you.

Dr. A. E. Horn (Closing the Discussion of His Own Paper.) — I thank you for the very kind way in which you have received my paper. As regards Professor Noguchi, I cannot now go into details about the alleged cases of yellow fever he examined in West Africa. We had no acute conditions, and in 6 months' observation not one case occurred. All that we could deal with was alleged cases who said they had yellow fever or had recovered from it. I think it would be much better to say we were unable to find any cases and that further investigation is needed as to the causation of the disease.

In regard to the mosquito screens, they have the advantage of doing away with the difficulty of using gauze. The alloy in gauze shortens its life, — in 5 or 6 months we found, in Africa, that the gauze went rotten especially near to the seacoast.

I agree with Dr. Deeks as to the necessity of individual treatment of cases of malaria.

We do not understand the exact nature of the action of quinine in malaria, and our results must guide us in treatment.

TROPICAL DISEASES OF COSTA RICA

LUCIANO BEECHE, M.D.

(Read by Title)

It is a very great pleasure for me to greet the International Conference on Health Problems in Tropical America, in the name of the Government of Costa Rica, which, in sending me here as its Delegate, demonstrates once more its traditional interest and spirit of co-operation in the humanitarian struggles of science against the diseases which afflict the Tropics. A good soldier in the cause of our health, the Government of Costa Rica has desired to take a part in this new council of war against the common enemy, in order to assume with enthusiasm the position which is assigned to it in the plan of attack to be agreed upon by this assembly, whose success has my sincerest wishes, and I am certain that it will be fecund in benefits to all the nations of the Caribbean and to Humanity at large.

The United Fruit Company renders a valuable service to our nations by its meritorious efforts directed toward vanquishing tropical diseases, and toward confining to their least radius of action the diseases peculiar to our climes. In effecting this, it is only just to acknowledge, it has not omitted pains or expense, as is fully evidenced today by the saving of lives and relief of suffering in its magnificent hospitals, and by its sanitary organizations and systems which are real models of their kind.

As in other countries of Central and South America, and in the West Indies, where it has established its banana industry, exploiting the agricultural wealth of immense zones previously uninhabitable and abandoned, the establishment of the United Fruit Company on the Atlantic coast of Costa Rica marked a new era in the hygienic conditions of Costa Rican territory. To its effort, its methods of fighting, is due principally the fact that we see today the old deadly regions of the coast converted into emporiums of production and activity. Of course, there has not been lacking in this work of progress — as there could not be lacking in this Conference

which will endeavor to intensify it — the voice of stimulus, of encouragement, and decided support of the Government and people of Costa Rica; and this Conference may be certain that our country and its Administration will second, with all the efficiency possible, the measures recommended by it for the practical objects pursued.

Prior to the year 1900, the year in which the United Fruit Company fully organized its operations in Costa Rica, the Atlantic coast and its natural outlet, Port Limon, were an immense swamp where yellow fever and malaria destroyed hundreds of people year after year, making agricultural enterprises and public works in those localities impossible. The railway line, constructed between the years 1874 and 1890, which connects the capital and the central table-land with Port Limon, has been literally strewn with corpses. Only the organizing genius and the iron will of Mr. Minor C. Keith, the builder of that railway, along with the progressive character of the Nation, could have finally established that artery which opened the doors of the Republic to the currents of commercial interchange and modern civilization. It was Mr. Keith, also, who later on — and then in combination with the future development of the United Fruit Company — carried out by means of contracts with the State the sanitation of Port Limon and other auxiliary works; while the Company, on its part, undertook, as its works of exploitation advanced, the hygienic improvement of the zones destined for banana cultivation, and their numerous villages, until it obtained the complete change to be observed today. Thanks to this, the former dominions of death have been gradually converted into centers of activity and life; and, owing to their splendid nature and conditions, they invite to new and constant scientific efforts made in order to arrive, in the near future, at the final victory against disease and suffering.

The symbol of the great campaign effected in Costa Rica by the United Fruit Company is without doubt its fine hospital which it maintains in Port Limon, and which, in addition to being the best in the country, is one of the best in the Tropics. Its Superintendent, Doctor Antonio A. Facio, a gentleman as full of intelligence as of energy, aided by a body of competent collaborators, worthily sustains the standard of honor which the Company has placed in his hands.

I shall now refer in brief terms to the diseases encountered in Costa Rica, whose study is of special interest to this Conference.

YELLOW FEVER

Its existence was noted on the Pacific littoral as early as 1853. Successive plagues, at times of great intensity, afflicted the region until 1903, when thanks to the measures adopted by the Government, the plague disappeared. It is curious to observe that in 1899 the disease was carried from Puntarenas, the Pacific port, to Alajuela, a city of the interior, 60 miles from the coast, situated at an altitude of 3,116 feet, where more than 100 cases occurred, with a mortality of 33%. At that period it was not yet known that the Stegomyia was the agent of propagation of the disease; and owing to this, the Government purchased the houses, clothing, furniture, and effects of the people infected, and ordered them to be burned, believing that in this manner the evil could be extirpated. Notwithstanding the fact that the Stegomyia exists on the central table-land, this was the only time that yellow fever was propagated in the interior of the Republic. The works of sanitation effected by the Government at the Port of Puntarenas, and the application of new methods of combat, eliminated yellow fever there, and since the year 1910 no other case has been registered.

Simultaneously, yellow fever was doing great damage in Port Limon and the Atlantic zone, but the Government and the United Fruit Company, intensifying the fight to which I have previously referred, totally defeated it. Neither have there been any more cases on that side for the last seventeen years. The campaign against the mosquito, the official sanitary services, and the hygienic methods adopted by the United Fruit Company, backed by our officials and citizens, have entirely driven out the plague which, in our scientific annals, appears only as historic data. The benefits thus obtained are imponderable, their economic effects are inestimable. Limon and its coast were a permanent antechamber of death; today they are places attracting human activity. However, there is much left to be done in the work of sanitation of this rich and extensive territory. Malaria, dysentery, and ankylostomiasis still rob labor of precious lives.

MALARIA

Although, practically, malaria does not exist in the cities, inasmuch as its geographical distribution is particularly confined to the ports and coasts, to localities adjoining these, and to the province of Guanacaste which adjoins Nicaragua, as also to the regions in the vicinity of the border of Panama — it is nevertheless a fact that during recent years this plague has been appearing in places in the interior where previously it had never existed; and the most serious thing is, that according to our official statistics, rather than diminishing, it tends to increase.

In the quinquennium from 1914 to 1918, inclusive, malaria killed 1,414 persons, or 3.14 per 1,000 of our population; and in the quinquennium from 1919 to 1923 inclusive, it killed 2,354 persons, or 4.89 per 1,000, which shows an increase of 1.78 per 1,000 in the deaths of the second period over those of the first, taking the progressive increase of the population into account. The cause of this enormous increase in the figures of mortality mentioned is probably due, it would appear to me, to the bad condition of many of the privies now in use.

It is true that the Department of Ankylostomiasis, to whose active propaganda is due the construction of a large number of privies, has given the instructions necessary to make them in such form that they can not be converted into breeding sites for flies and mosquitoes, but frequently the people do not follow the rules laid down by this Department. The sanitary installations are abandoned as soon as the instructors leave the localities, the organic matter going to the bottom of the holes, and rain or the filtration from the subterranean strata fills them with clean water, which constitutes a good agency for the development of Anopheles.

I believe that if the Department of Ankylostomiasis could utilize the services of doctors, who, as such, would have more prestige and greater moral influence with the people than the employees selected at random whom this Department now uses, the campaign undertaken would be more fruitful in practical results. Unfortunately, this Department employs only one doctor — its Director.

Black-water fever exists in the most infested malarial

regions, and especially on the Atlantic zone. The usual kinds of malaria fevers are the tertians and the estivo-autumnal; the quartans are rare. In order to combat malaria, several years ago, the Government decreed customs franchise on all salts of quinine, and gratuitous distribution is effected by the district medical offices for account of the Public Treasury and of the Municipalities.

In regard to the malarial index, I must say that it is not yet possible to supply data in this respect, as the disease has not yet been the object of special study in the various regions of the country.

SPRUE

It was Dr. Carlos Pupo who was the first to call attention among us to this disease, whose treatment by means of a diet free from carbohydrates — as recommended by Ashford — is giving excellent results.

The disease holds sway in the entire country, but especially in the cities, where it sometimes takes on severe forms which are rapidly conducive to "cachexia," whereas in other cases only its presence is observed, during entire years, in the course of which are discovered periodically the characteristic lesions of the mucous membrane of the mouth, which alternate, or appear simultaneously, with abundant frothy diarrhea of a light-yellow color, so characteristic of this disease.

The bacteriological examinations which, up to the present, have been made in order to isolate the "*monilia psilosis*" described by Ashford as the specific cause of the evil, have been negative, but the treatment in one case by vaccine has been favorable.

In Costa Rica, where a great variety of fruits and vegetables abound, we have been able to observe the brilliant results obtained by the elimination of starches and sugars.

FUNGUS

We have found and isolated the "aporotrichum" described by Beurmann and Gougerot, in persons who have pricked themselves while sewing the sacks of black beans — the legumes which constitute the main item of the daily food of our peons. We have also been able to observe some cases of "blastomycosis" and of "madura" foot.

DYSENTERY

This is of an endemic character throughout the whole country. During the last 10 years, 2,552 persons have died from it. We calculate that 2% of the patients die from the disease. The largest number of the cases are of amebic origin. There are also cases of dysentery produced by balantidiums and trichomonas, but they are not so frequent as the amebic. Since therapeutics has been benefited by the marvellous treatment discovered by Rogers, the number of deaths from dysentery has been decreasing year by year, and abscesses of the liver have become very rare.

Bacillary dysentery has been found of an epidemic character in Puntarenas (on the Pacific coast) and Escasú (in the interior). At the latter place, violent cases were noted, deaths having occurred in 48 hours. All the cases were produced in houses situated along a stream.

ANKYLOSTOMIASIS

It was the illustrious Costa Rican physician, Carlos Duran, who first discovered this pestilence in Tropical America, and the Government of Costa Rica was the first among these nations to organize the fight to eradicate it by means of technical commissions and popular conferences. Subsequently, the Rockefeller institution established a laboratory for gratuitous examinations, and organized other commissions of sanitary propaganda, which are actively engaged in instructing the people regarding the prophylaxis of the disease, and in distributing the medicines for their cure.

According to official statistics, 50% of the population is infected with uncinariasis. Agricultural laborers are the principal victims of the plague, and it will not be until the campaign is intensified that we shall be able to reduce it so far that it will be no longer a danger, because I agree with Ashford that to eradicate it entirely will never be possible in the Tropics.

OTHER DISEASES

As in the case of yellow fever, cholera-morbus — which made its last raid in 1856 destroying a fifteenth part of the total population — and small-pox, whose last plague dates

from 1891, are at the present day only a historic conception in the country.

Leprosy is reduced to the 40 cases isolated in the lazaretto.

Among the most powerful agents of mortality, especially infantile, are the diseases produced by intestinal parasites, the following being found in the order of their frequency: ankylostoma, tricocephalus, amebas, ascaris, trichomonas, anguilullas, balantidiums, tenia solium, tenia medio canelata, tenia nana, and dipylidium caninum.

Some years ago, there was a case of intestinal Bilharziosis in an individual coming from Venezuela. The patient was deported from the country, and the disease was not propagated.

Bubonic plague has never been present in our country.

SANITARY ORGANIZATION

The Government of the Republic maintains at its expense some 30 district medical offices, services of venereal prophylaxis in some cities, port doctors, quarantine services at La Uvita — an islet in front of Port Limon — a recently established service of public assistance, a department of school sanitation, and an infantile clinic in the capital; and devotes yearly amounts to the campaign against ankylostomiasis, purchase of drugs, for unforeseen campaigns against other epidemics which may arise, vaccination against smallpox, and services of injections and vaccines. All these branches come under the management of the Department of Hygiene and Public Health.

In addition to the above, the State gives subventions to numerous charitable institutions, such as the Las Mercedes Asylum (lazaretto), the Carit Sanatorium (for tuberculosis), the Carit Lying-in Hospital, the Poor Asylum, 11 hospitals, 6 orphanages, the Infant's Asylum, kitchens for poor school children, several establishments for distributing milk to poor children, the Limon Infantile Sanatorium, etc., etc. The control of these organizations is effected through the Executive Committee of Charity.

At present, there are more than 100 villages with waterpipe installations in the Republic.

Everything points, therefore, to the sanitary improvement of Costa Rica, and in this direction, the Government, the

people, and its medical corps are earnestly engaged. Particularly, the diseases typical of the Tropics may be eradicated in the near future, inasmuch as this aspiration is entertained strongly by the nation as a whole, and is closely connected with the future agricultural and industrial evolution of the unhealthy regions of the territory where, precisely, the fertility of the soil and the potency of production are greatest.

The United Fruit Company is our principal ally in this work of national progress, which, at the same time also favors its own interests, thus demonstrating that coöperation is the foundation for the mutual success of natives and foreigners.

The International Conference on Health Problems in Tropical America, convoked under the auspices of the Company, will undoubtedly set forth the new technical operations which are to conduce to the complete defeat of the adversaries which we still have before us in this interminable duel of Science and Progress against Disease and Death.

It would be extremely gratifying to me to be the bearer to my Government and my country of the watch-word which this General Headquarters may give, and which we shall faithfully act upon.

Before concluding, I wish to confirm my faith in victory and to renew my cordial wishes for the success of our deliberations, in which scientific effort we shall be sure to feel stimulated by the love with which we are all inspired toward the beautiful region of the Tropics, and by that more ample love for the welfare of Humanity.

NOTE ON THE USE OF A BISMUTH SALT IN SUBSTITUTION FOR ORGANIC ARSENICAL PREPARATIONS IN THE TREATMENT OF YAWS (*FRAMBŒSIA TROPICA*) WITH SPECIAL REFERENCE TO THE FINANCING OF AN ANTI-YAWS CAMPAIGN

A. R. Paterson, M.B.

There is good reason to believe that Yaws is most frequently acquired either by direct contact with an infected person, e.g., as between mother and child, or indirectly as the result of the contamination of some abrasion by flies which have recently been in contact with an infected person. The disease, when incident to any degree, is always associated with a markedly insanitary environment; the causal organism, the *Spironema pertenue*, *Castellani*, 1905, is always present in the secondary granulomatous eruption, the exudation from which affords an attractive bait to any non-bloodsucking fly; and as the populations among which the disease occurs are not only barefooted, but are otherwise lightly clad, most of the healthy individuals present, as a rule, in the form of cuts or abrasions, especially in the neighborhood of the shins and ankles, suitable sites for the implantation of the organism by any fly which may alight thereon. The infection is possibly conveyed by bloodsucking flies of the genus *Stomoxys*, by ticks of the genus *Ornithodorus*, by insects such as lice or bed-bugs, or by contact with utensils, clothes or huts which may recently have been used by an infected person.

The conveyance of the infection during sexual intercourse doubtless happens in a certain number of instances, but there is no reason for regarding these cases as other than incidental or for placing the disease within the category of true venereal infections. Ante-natal infection has not so far been recorded.

Assuming, therefore, that the only reservoir of the infecting organism is man, and that bulk infection takes place, as a rule, only under conditions where close contact either

with infected persons, fomites or flies is unavoidable, 4 methods by which prevention of the disease and its eradication from any particular district might be secured, suggest themselves. These methods are:

1. By immunizing the population
2. By raising the standard of sanitation
3. By segregation of the infectious members of the community
4. By rendering as large a proportion of the infectious members of the community as possible, non-infectious

If practicable, these methods might be used either singly or in combination.

But the 1st method is not at present feasible; no practical method of immunizing the individual is known.

The 2nd method, if carried sufficiently far, would doubtless in the long run be effective, but dependent as any radical improvement in the general sanitary environment of backward peoples in the Tropics must be, not only on their economic condition, but on the progress of education and the alteration of their outlook on life, it is not in this instance a method to which we can look for immediate results.

The 3rd method, segregation of the sick, is, at least in any very heavily infected area, totally impracticable, both for economic and for other reasons.

Fortunately the 4th method presents hope of success, as in any of the organic arsenical preparations we have a drug the exhibition of which on 1 or 2 occasions results as a rule in the complete disappearance of the secondary granulomatous eruption of Yaws within a few days, and almost certainly renders the patient either non-infective or at least very much less infective for a considerable period, even when a complete cure is not effected. Also, as the relief which is afforded is not only remarkable, but practically immediate, there is not, at least among the African natives of Kenya, any difficulty in securing the attendance of those sick who are able to walk and are within a reasonable distance of an hospital or dispensary.

It would therefore appear that, in order to secure the eradication of the disease from any district, all that is necessary is so to multiply the facilities for treatment, and

so to increase the accessibility of these facilities, as to insure that all cases existing in the district shall receive treatment so far as possible simultaneously; also to make provision for the treatment of all other persons who may be incubating the disease, as soon as recognizable signs present themselves, and for the treatment of any cases which may happen to relapse at a later date.

But to carry out a campaign on these lines 2 things are necessary: (1) a sufficiently large staff of persons capable of administering intramuscular injections, and (2) a sufficiently large supply of a more than usually expensive drug. At least that was the position when we were still dependent on the organic arsenical preparation for the treatment of Yaws, and it is possible that our experience with an alternative drug may be of some interest.

In the Colony of Kenya, until recently known as the East Africa Protectorate, Yaws has been present for many years past. But it was not till after the conclusion of the World War — when for the first time it became possible to make provision for treatment in some of the more outlying districts with the organic arsenical preparations — that it became obvious that the incidence of the disease was very considerable indeed, and that medical relief and possible action for the control of the disease was urgently required.

Toward the end of 1920, therefore, a campaign for the treatment of the disease on a large scale was instituted in several districts by the Medical Department, and during the following year over 7,000 persons received treatment, the drug used being, in the first instance, Galyl, and later, Novarsenobillon. In 1922 the campaign was extended, and in that year over 25,000 cases were treated. But the purchase of Novarsenobillon for the treatment of these 25,000 cases cost over £4,000, while on a conservative estimate it appeared that at least 60,000 cases of the disease remained to be dealt with, and it was not clear how financial provision was to be made for any further extension of the campaign.

Fortunately, about this time, the attention of the Department was drawn by Dr. Andrew Balfour to the fact that a salt of Bismuth was being used with some success in the neighboring Tanganyika Territory, and Dr. Shircore,

Deputy Principal Medical Officer of the Tanganyika Medical Service, very kindly provided us with all the information which was at his disposal, with regard to its use and preparation. The data so provided were then passed to the workers of the Chemical Research Department in Nairobi, and after a considerable amount of experimentation and research they produced for our use a salt, Bismutho-tartrate of Sodium and Potassium, which contained approximately 54% of bismuth, the percentage which, in the only literature at our disposal, was noted as having given successful results. The salt so prepared was then tested against rabbits, and as its toxicity appeared to be less than that used by Sazerac and Levaditi in France, it was next tried on a number of cases of Yaws. The results were excellent, and appeared to be in no way inferior to those previously obtained with Novarsenobillon.

Bismutho-tartrate of Sodium and Potassium has now been in use in Kenya for over 18 months, that is to say, since about January, 1923, and during that time it has been the only drug used by us in the routine treatment of Yaws. The complete figures for the number of cases in which it has been used are not at the moment available, but it may be noted that in 2 districts, alone, over 36,000 cases were treated with this preparation during 1923.

The dose for an ordinary adult is 3 grains given intramuscularly in 2 cc. of distilled water. For infants and for old people a smaller dose is used. The salt appears to keep well, is easily prepared for administration, and if due care be taken can safely be administered by a trained dresser or hospital assistant.

The majority of cases are treated, not at central institutions, but either by medical officers while on tour in their districts, or by trained native dressers at small field dispensaries. In all cases it is given by intramuscular injection into the buttocks, and though the injection is followed by a certain amount of pain, this would not appear to be notably more marked than is the case with Novarsenobillon, and it does not in any case deter patients from attending for treatment. Abscess formation has been exceedingly rare. The only precaution which it is necessary to emphasize is, that care must be taken to insure that the dose of 3

grains is never exceeded, and further to insure that a suitable reduction is made in the case of children and old people, as it must be remembered that bismuth given intramuscularly is an exceedingly active drug and that any excess may be followed by toxic effects, the most notable of which is a stomatitis which may on occasion be exceptionally severe.

The great practical importance, however, of the introduction of this preparation of Bismuth lies in the fact that compared with the arsenical preparations it is cheap.

The usual dose of Novarsenobillon was .6 gramme and cost three shillings. The cost of the usual dose of the Bismuth preparation is $\frac{1}{10}$ of a penny for material, plus the cost of preparation; as, however, preparation is carried out in the local government laboratory, and does not occupy the whole time of a chemist, it is difficult to estimate how much should be added to the cost on this account.

If, however, consideration be given to the fact that, for the purchase of Novarsenobillon for the treatment of 25,000 cases of Yaws in 1922, it was necessary to expend over £4,000, while the purchase of materials for sufficient of the Bismuth salt for the treatment of the same number of cases would not have exceeded £15, it is obvious that even if the whole-time services of a chemist had to be provided for, the saving would still amount to well over £3,000.

DISCUSSION

Dr. H. J. Nichols (Opening the Discussion).— I think Dr. Paterson is to be congratulated on carrying out this work, which affects the health of the people under his charge to such an extent; and the fact that the price of the work can be reduced by 3,000 pounds certainly makes it more practical.

In 1910 it fell to my lot to be the first to bring *Treponema Pertenue,* the cause of Yaws, into contact with salvarsan. I was detailed at the Rockefeller Institute, and Dr. Flexner had just received some salvarsan from Frankfurt. We had a case of Yaws in a colored man in a garrison near New York, and it was possible to transfer this organism to a monkey, and then to a rabbit, and carry on therapeutic work in the rabbit. I was able to show that this spirochæte is really twice as sensitive to arsenical drugs as is pallida. This particular strain was taken to Professor Ehrlich and the results were confirmed in Frankfurt.

It is much easier to cure yaws than syphilis, provided you accept the difference in the diseases. It seems to me possible that a little further animal experimentation in Bismuth might lead to a clearer understanding of this sort; but when the practical results are so good, there is not much temptation to indulge in experiments. However, the philosophy of medicine always is worth cultivating, and I think it would be very nice to know whether these patients are cured or not. Clinically speaking, they are cured; spirochætically speaking, they will be cured if the last spirochæte is dead. As a practicing physician, I think we ought to use the word cure in that sense, in syphilis, in amoebic dysentery etc.

What is the relation that yaws has to syphilis? Some of our naval medical officers have been doing a great deal of epidemiological work out in the East; some think yaws is simply syphilis under tropical conditions and that yaws protects against syphilis.

The organism of yaws is different from that of syphilis, in its effect on experimental animals. Through the kindness of workers in the Canal Zone, I have had some rabbits sent to Washington, D.C., infected with yaws. In inoculation of the scrotum, syphilis will go on to a very definite ulceration, while the yaws have been very difficult to maintain. A small papule forms, with secondary nodules around the primary — which never occurs in the case of syphilis. In syphilis you can transfer this disease from the lymphatic gland. In yaws it is very difficult to do that. We have lost a number of strains in yaws, simply because we could not keep them going in the rabbit, while the syphilitic organisms each time would make 100% of "take."

In animals these diseases are very different and I prefer to agree with Dr. Castellani, who discovered this organism, that the diseases are distinct. I believe Dr. Wilson has been doing some of this kind of work in Haiti.

Dr. Paul W. Wilson. — The history of Yaws in Haiti is rather interesting. Within about 20 years after the discovery of Haiti by Columbus, the first negro slaves came into that island, and within 100 years had practically replaced the Indian population. It is a much mooted point whether syphilis was taken to Europe from Haiti by Columbus' crew or not; but the fact remains that the Indians were displaced by the negroes, and whether that was due in a measure to the fact of the negroes having had yaws, and perhaps a relative immunity to syphilis therefore, must always remain a matter of pure speculation.

Early in the slave days, yaws houses were established and any slave contracting the disease was isolated, and he remained in

isolation until he was well, or rotted to death from secondary infections. This may account for the fact that yaws today, in Haiti, is generally regarded as a disease of shame, and for that reason the patients try to conceal their condition as much as possible. Certainly in the towns there has been a quarantine against all yaws cases which dates back as far as one can remember.

Haiti has been considered to be the most syphilitic island in the world, but from recent investigations this would appear to be most erroneous. During my first year in Haiti I saw 28 cases of early yaws, and these were usually found on the trails outside of town. Only 1 case came to the hospital, although there were many tertiary cases under treatment during all this time, but these were popularly considered as syphilis. I urged all of these 28 cases to come to the hospital, but only 1 of them came. Then I found out that the town people were not in the habit of allowing these people to come into town, and it is interesting to know that they seldom make a mistake in diagnosis.

I was looking for aortitis and aneurism, and I did not find any in the country population. But in the towns, i.e., in this one city of Jacmel, I found about 12 cases of aortitis, 3 cases of aneurism, 1 case of tabes, and 2 cases of hereditary syphilis. In the country population no cases of tertiary syphilitic circulatory or nerve lesions or hereditary syphilis have as yet been noted. In connection with Dr. Paterson's remarks on gangosa, it would appear that yaws is the cause of gangosa in Haiti.

The economic loss from yaws in Haiti is enormous. In the country, where many of these families are a long distance from the city, one often finds several members of one family suffering from crab yaws, and among these people any interference with their powers of locomotion works a real hardship. It is considered that most of the beggars in Haiti, and there are a great many of them, are cases of tertiary yaws.

I started out 9 months ago to make a survey of the prevalence of yaws in the arrondissement of Jacmel. That survey has been frequently interfered with on account of insufficient sulpharsphenamine, this lack being due solely to insufficient funds with which to buy the necessary amount of arsenicals. Since October I have found 1,100 cases of early yaws and about 4,000 tertiary cases in a population of 50,000. At a conservative estimate, these figures could be easily doubled or trebled, as I have been able to work on this yaws survey only about ⅓ of the time on account of insufficient supplies. With a population of 2,500,000 in Haiti, one can readily appreciate what a yaws campaign will mean, from both the standpoint of the Haitian countryman and

that of the Government, which has to pay the bill. At present the Government is supporting a large number of tertiary yaws cases who are filling beds in our hospitals to the exclusion of other patients who should also have hospital care. I wish to thank Dr. Paterson for the report of his work in Africa, and I believe that the administration of bismuth salts in our yaws campaign in Haiti will solve a problem which has been practically insurmountable up to the present time.

Dr. Aldo Castellani.— I was extremely interested in the communications made by Dr. Paterson, by Dr. Nichols and by Dr. Wilson. I agree with Dr. Paterson about the very great importance of a yaws campaign as an economic factor in the development of a colony. When I went to Ceylon in 1903, there were large districts of the Island in which it was practically impossible to get any labor; 80% of the children were suffering from Yaws, and of the adults about 30%, were suffering from the late manifestations of the disease. The number of cripples was simply appalling. All that is now changed.

I am in complete agreement with what Dr. Nichols has said on the experimental investigation of yaws. Dr. Nichols was the first to carry out a complete scientific experimental investigation of the malady in the lower animals, and his investigation has remained classical. As regards diagnosis when the patient is in the generalized granulomatous eruption, there is absolutely no difficulty in making it. I think that when you have once seen a typical case of yaws, in the secondary stage, you cannot forget the clinical picture of the disease, particularly the large numerous granulomata all over the body, covered with thick yellow crusts. The difficulties in diagnosis come in the late manifestations of the disease and, according to certain authors, also in the very first stage of primary frambœsial sore. As regards the primary sore, any one who has had long experience with yaws will agree, however, with me that it is quite different from the primary sore seen in syphilis. First of all, it is practically never found on the genital organs. The lesion is a small granuloma which fairly rapidly increases in size, and later on shows all the characteristics of the granulomata of the secondary eruption; the primary sore is identical with the granulomata of the secondary eruption. In the late manifestations of the disease, certain cases certainly present difficulties in the diagnosis, especially with syphilis. I should like to call attention to the following differential characteristics:— First of all, all the lesions of yaws have a tendency to become hypertrophic; for instance, both in yaws and in syphilis a circinate type of eruption is not rare, but the circinate eruption

of yaws, which is also known as "ring-worm" yaws, is quite different, the rings being very much thicker. This hypertrophy is also in evidence in the ulcers and in enormous scars. Other differential diagnostic points are the following:

In yaws there is very often severe pruritis; this is absent in syphilis. Another rather interesting differential characteristic is what I call the mercury test. Mercury is practically useless in yaws. It must also be remembered that yaws is never congenital; you see a native woman covered with profuse granulomatous eruption of yaws, and the baby born is perfectly healthy.

As regards treatment, the history of the modern methods of treatment in yaws is the following: Dr. Nichols was the first to treat experimental yaws with salvarsan, and — I think I may say independently — Strong in the Philippine Islands and I in Ceylon, administered salvarsan to human cases of yaws and obtained very good results. Later, instead of salvarsan, we used neo-salvarsan. These drugs give wonderful results. After 2 or 3 injections all the symptoms disappear, but in a certain number of cases the cure is purely a clinical one. The infection remains latent, and sooner or later will flare up again.

As regards the Bismuth treatment advocated by Dr. Paterson, I am in favor of it. I think Bismuth should be substituted for salvarsan and neo-salvarsan, as, while it is equally efficacious, it is cheaper and is given by intramuscular injection. There are cases in which for various reasons injections cannot be given, and I recommend then a mixture I devised some years ago in Ceylon, the formula of which is:

Tartar emetic	gr.i.
Potass. iodide	℥i. (one)
Sodii Salicyl	gr. x
Sodii bicarb	gr. xv
Aq. a.d.	℥i.

An ounce is given 3 times a day, diluted with 3 times as much of water. This mixture is, pharmocologically speaking, very inelegant and often contains a precipitate. The addition of a drachm of glycerine and a drachm of syrup will keep it clear and prevent the formation of the precipitate. The active drugs in the mixture are the potassium iodide and the tartar emetic; the salicylate of soda does not influence the yaws lesions in the least, but seems to hasten the disappearance of the thick crusts. The bicarbonate of soda tends to prevent the symptoms of iodism, and decreases the emetic properties of the mixture, in this way rendering possible the administration of massive doses of potassium iodide and of large doses of tartar emetic.

Dr. A. R. Paterson (Closing the Discussion of His Own Paper).—The question of the number of doses of Bismuth which may be required to effect a cure has been raised. I can only say that, in regard to this matter, we have at present practically no information and that, as the disease is one in which recrudescence in the untreated is a not uncommon occurrence, it will be some years yet before an opinion of any value can be expressed. The point of importance is that in the Bismutho-Tartrate of Sodium and Potassium we have a drug which is not only cheap, but causes the rapid disappearance of distressing and disabling conditions, and almost certainly renders the patient much less infective.

The question of the method of administration has been raised. I can only say that we have only used the intramuscular route.

In conclusion, gentlemen, I wish to thank you for the kind way in which you have received this paper, and also to record my indebtedness to the Colonial Office in London for permission to recount some of the work which has been done by my colleagues in the Kenya Medical Service under the direction of my Chief, Dr. J. L. Gilks.

NOTES ON THE INCIDENCE OF PLAGUE IN KENYA IN RELATION TO A RECENT MIGRATION OF RODENTS, AND ON AN EXPERIMENT IN ERADICATION CARRIED OUT BY A NATIVE TRIBE

A. R. Paterson, M.B.

Geographical Situation of Kenya

The Colony and Protectorate of Kenya, until lately known as The East Africa Protectorate, is situated between latitude 5° N. and 5° S. and is bounded on the east by the Indian Ocean and Italian Somaliland, on the north by Abyssinia, and on the west by the Victoria Nyanza and the Uganda Protectorate. The Colony and Protectorate comprise an area of some 245,000 square miles, and the country presents the greatest variations in climate and altitude. The coast on which is situated the port of Mombasa is hot, moist and tropical, while further inland there is a great plateau — the Highlands of East Africa — varying from 4,000 to 8,000 feet in height, where sub-tropical or almost temperate conditions prevail. Traversing the country from S. E. to N. W. is the Uganda Railway, connecting Mombasa on the Indian Ocean with Kisumu on the Victoria Nyanza. This railway was completed towards the end of 1901. Kisumu, the Lake Terminus of the railway, is at an elevation of 3,500 feet.

History of Plague in the Countries Bordering on the Victoria Nyanza

The existence of plague in Central Africa was determined bacteriologically for the first time by Koch and Zupitza, in 1897, in Uganda,* but there is considerable reason to suppose that even then the disease was not a new one in these parts. Simpson, in a report dated 1915,† states that, "The evidence as to plague having existed in Uganda for many years before 1894, is such as to establish the fact beyond dispute."

* "A Treatise on Plague," W. J. Simpson, *Camb. Univ. Press.*

† "Report on Sanitary Matters in the East Africa Protectorate — Uganda and Zanzibar, 1915," W. J. Simpson (Colonial Office, African No. 1025).

In Kenya, on the other hand, there is no definite evidence with regard to plague till 1902, in which year cases were diagnosed at Nairobi on the Uganda Railway, midway between the Victoria Nyanza and the coast, while on the Kenya shores of the Victoria Nyanza plague remained unknown till 1904, when cases were for the first time discovered at Kisumu. Today the disease is endemic over a large area of the Kikuyu country in the Highlands of Kenya, and also over a large part of the Nyanza Province, of which Kisumu is the capital. It is to certain observations made with regard to the extension of plague which has taken place in recent years in the latter area, that I wish to direct your attention.

DOMESTIC RODENTS OF KENYA

Only three species of the *Rodentia* occur as domestic parasites in Kenya. These are:

1. { *Rattus rattus kijabius.* / *Rattus rattus frugivorous.* — These are sub-species or geographical races of *Rattus rattus rattus*, the old "black" rat of England and the East, formerly known as *Mus rattus* — the "black" rat. *R. r. frugivorous* is distinguished by the lighter colouration of the belly fur, and is the sub-species which, in parts of India and in the islands of the Mediterranean, is still to be found living a free, wild life in the open. In Kenya, however, *R. r. frugivorous* occurs only as a domestic rat living side by side with *R. r. kijabius*, which is a slightly darker-coloured variety. Neither *R. r. kijabius* nor *R. r. frugivorous* is ever found apart from human habitations in Kenya Colony.

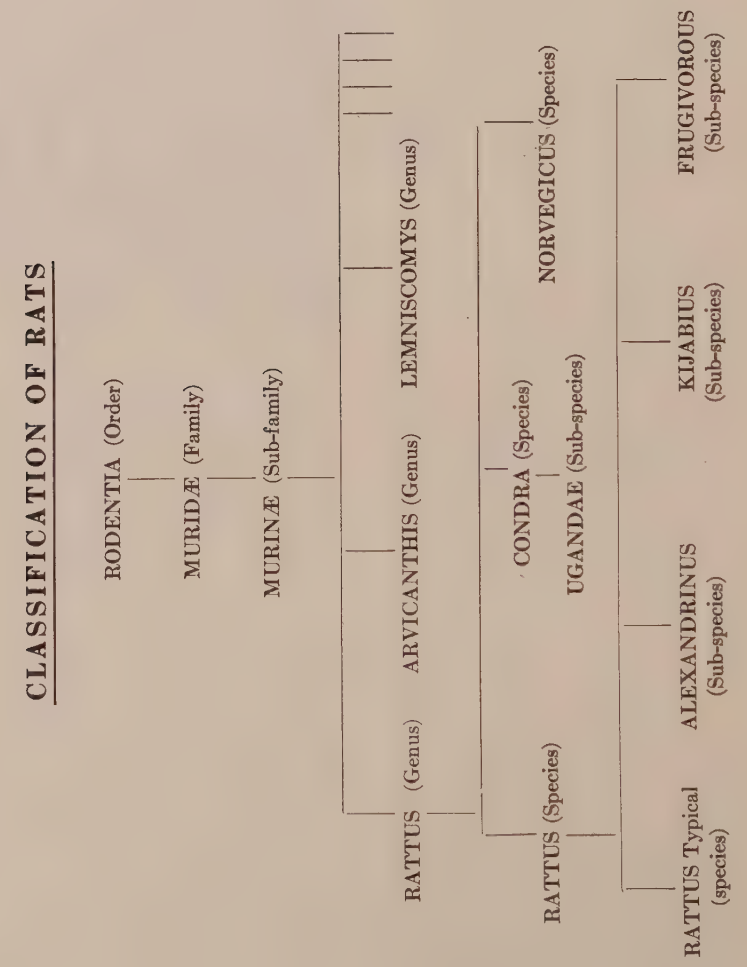
2. *Rattus coucha ugandae.* This is a much smaller rat than *Rattus rattus*, and on account of the fact that the female is furnished with 10 pairs of mammae (in contradistinction to the 5 pairs characterizing *Rattus rattus*) it may be referred to as the "*multimammate*" rat. In certain parts of Kenya it is still the only species to be found in native huts. It was probably at one time the only domestic rat to be found in Kenya, but in recent years it would appear to have been driven out of the huts in many areas and replaced by the "black" rat, *Rattus rattus*. *Rattus c. ugandae* occurs not only as a domestic rodent, but as a wild free-living species.

3. *Rattus norvegicus.* This species, formerly known as *Mus decumanus*, is the common "brown" rat of England — the "Hanoverian" rat. It is to be found in considerable numbers in Mombasa on the coast, but would not appear to have spread beyond the confines of the small island on which Mombasa is situated. It is never found "up country."

Of the above-mentioned three rodents, *Rattus norvegicus* is comparatively unimportant, being limited to one town. *Rattus rattus*, on the other hand, has now a wide distribution: it is the only species which so far has been found infected with plague, — and plague has never been found in those parts of the country where this rat has not yet penetrated.

Rattus coucha ugandae, the "multimammate" rat, has not yet been found infected with plague, and in those parts of the country where it is still the only "hut rat," plague is unknown.

The place of these rats in the general classification of the *Rodentia* is shown in the following table: —



PROFESSOR SIMPSON'S NOTE ON CONDITIONS IN 1913

Writing in 1913, Sir William Simpson, who made an extensive tour through the country in that year, said*:

> In some of the Kavirondo districts the more intelligent natives associate the appearance of plague with the advent of a new species of rat, which they call the Kisumu rat, and which they declare is the only one that suffers from epidemics of rat disease.

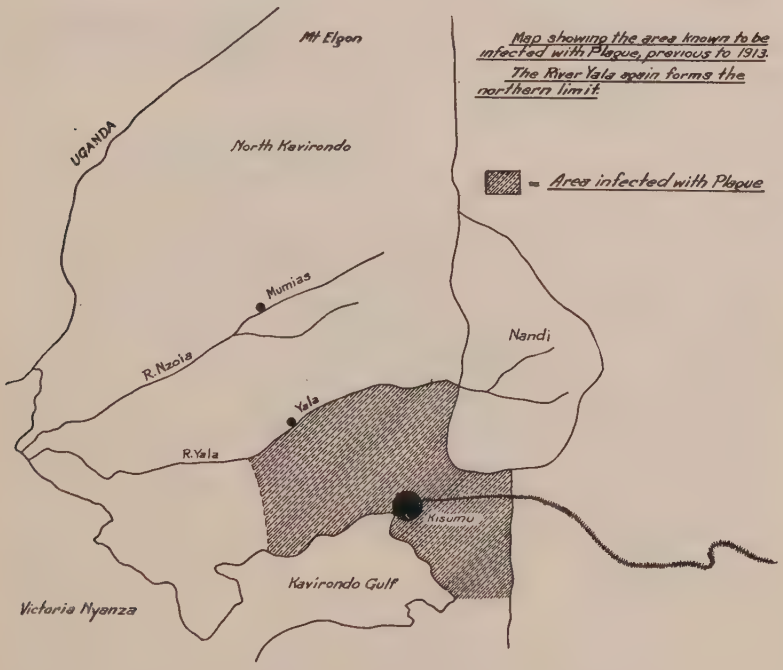


FIG. No. 1.

> They have always had the field rat and the small, black house-rat, but the large, dark-brown rat which is found in the houses in Kisumu, is, they assert, a new importation. It has reached as far as Yala in the north, but not Mumias, and Yala appears to be the northern limit of the prevalence of plague in this district.

The "large, dark-brown rat" mentioned by Professor Simpson is *Rattus rattus kijabius* and *Rattus rattus frugivorous*. The "small, black house-rat" would appear, as will be shown later, to have been *Rattus coucha ugandae*. The

* "African," No. 1025.

"Kavirondo" districts are the districts north of Kisumu in the Nyanza Province.

Figures 1 and 2 show the distribution of plague and of the "black" rat, *Rattus rattus*, as they were found, according to the native reports given to Professor Simpson in 1913.

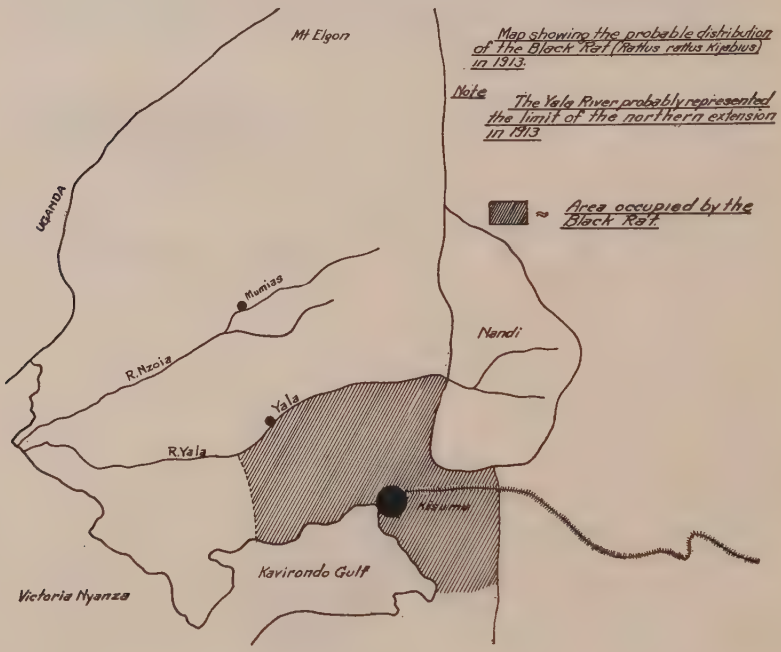


FIG. NO. 2.

In 1916 and 1917, when I was stationed at Kisumu, though there were numerous outbreaks of plague in the country between Kisumu and the Yala River, no reports were ever received of any outbreaks further north, and it was only in 1919 that plague was reported for the first time as having broken out to the north of the Yala River. The occurrence was at once investigated by a medical officer, who found that a considerable epidemic was in progress throughout the area between the Yala River and the government station at Mumias, but no observations with regard to rats are noted as having been made at that time.

In 1921 outbreaks were still occurring, and shortly afterwards — during a tour through the district north of the

Yala, on which I was accompanied by the Administrative Officer of the District, Mr. H. B. Montgomery — having in mind Professor Simpson's Report of 1913, we made some inquiries as to the history of the disease and observations as the species of rat infesting the houses. Everywhere we went in the infected area, the only rat we could find in the huts was the black rat, *Rattus rattus*, and everywhere we were told the same story by the natives. Both plague and the black rat, they said, were new to that part of the country.

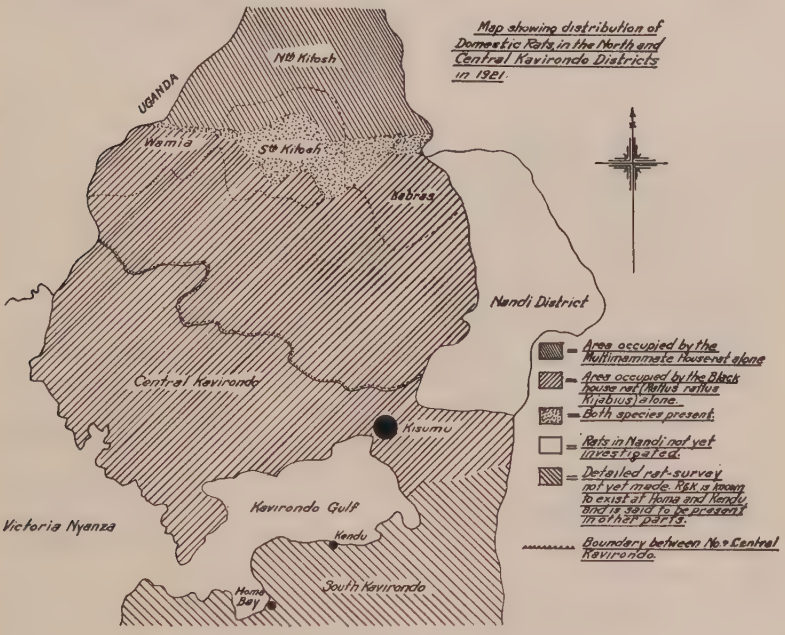

Map showing distribution of Domestic Rats in the North and Central Kavirondo Districts in 1921.
Nth Kitosh
UGANDA
Wamia
Sth Kitosh
Babras
Nandi District
Central Kavirondo
Kisumu
Kavirondo Gulf
Victoria Nyanza
Kendu
Homa Bay
South Kavirondo
= Area occupied by the Multimammate House rat alone
= Area occupied by the Black house rat (Mastomys rattus Rhabdus) alone.
= Both species present.
= Rats in Nandi not yet investigated.
= Detailed rat-survey not yet made. R&K is known to exist at Homa and Kendu and is said to be present in other parts.
Boundary between No & Central Kavirondo.

Fig. No. 3.

Previous to 1919 the disease had not been known to them north of the river Yala, and though they did not in all cases associate the disease with rats, they were always definite in their assertion that the invasion of their villages by the black rat had occurred some time before plague broke out among them. In the most northerly part of the district, however, towards Mt. Elgon, from which no reports of plague had been received, the disease proved on investigation not only to be absent, but unknown, and on examination of the huts for rats, only the small multimammate rat, *Rattus coucha*

ugandae, was to be found, and the black rat was not known to the natives even by repute.

The observations referred to were made during a hurried trip, by car, of only a few days' duration over a very large area of country, and it was felt that the matter was worthy of further and fuller investigation. Later in the year, therefore, Mr. W. R. van Someren, who had been collecting elsewhere in the Colony, was engaged by Government to make a

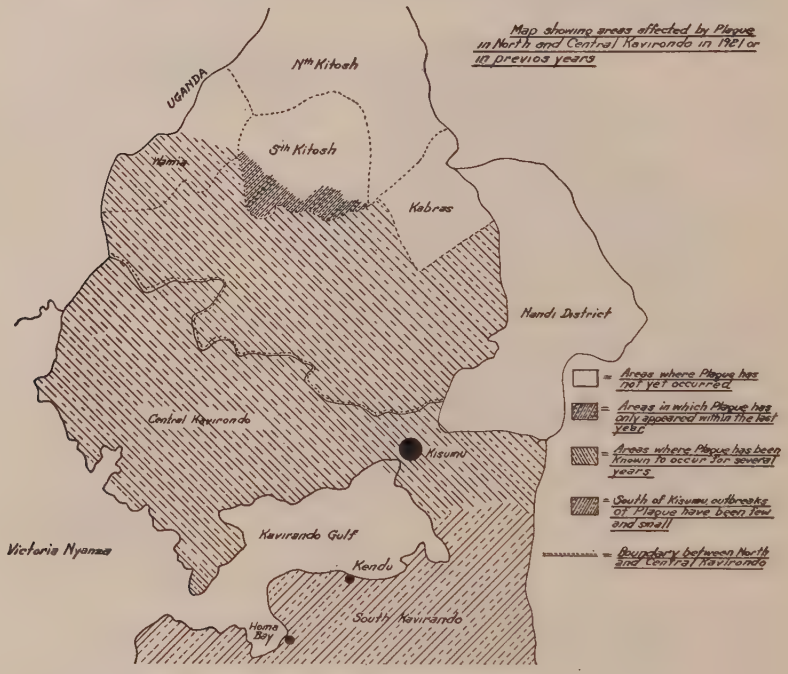

Map showing areas affected by Plague in North and Central Kavirondo in 1921 or in previous years
UGANDA
Nth Kitosh
Sth Kitosh
Nandi
Kabras
Nandi District
Central Kavirondo
Kisumu
Victoria Nyanza
Kavirondo Gulf
Kendu
South Kavirondo
Homa Bay
= Areas where Plague has not yet occurred
= Areas in which Plague has only appeared within the last year
= Areas where Plague has been known to occur for several years
= South of Kisumu outbreaks of Plague have been few and small
= Boundary between North and Central Kavirondo

FIG. NO. 4.

detailed survey of the distribution of the various small mammals of this area. Mr. van Someren spent 6 months in the district, and the result of his survey as regards *Rattus rattus* and *Rattus coucha* are shown in Figure 3. If this figure be compared with Figure 4 ,which was compiled from material supplied by Dr. P. F. Nunan, who was then Medical Officer of the district and constantly on tour throughout the area, it will be seen that with the exception of one small area the distribution of plague and the black rat coincide, that the

most recent area to be infected is just south of the line of advance of *Rattus rattus*, and that the area which is not yet invaded by *Rattus rattus* is free from plague.

During the course of his 6 months' survey, Mr. van Someren made careful enquiries as to the length of time the black rat had been known to the people, and always the reply, "north of the Yala River," was to the effect that the ousting of the multimammate by the black rat had taken place only within the past few years.

During the past year (1923) information has been received from the Medical Officer of the district, to the effect that the black rat has made further strides and that areas which were free at the time of Mr. van Someren's survey are now infested by *Rattus rattus*.

It is of interest to note that though there has been for many years a trade route running north from Kisumu, through the infected district south of the Yala, and on through an uninfected area to another infected district in Uganda, the spread of plague has not in this instance been along that trade route. The advance of *Rattus rattus* has been a comparatively slow one, along a broad and extended front from hut to hut and from village to village, across country, and it is only in his wake that plague has appeared. For many years before 1913 there had been free movement of people and of merchandise from infected to uninfected districts, but such traffic has never in this area resulted in the establishment of the infection. Had traffic been responsible, the spread would have been much more rapid and the northern villages of Kavirondo would not have had a respite of 10 years while *Rattus rattus* was covering 50 miles.

The Rat Destruction Campaign

That part of the Nyanza Province which lies to the north of Kisumu is divided into 2 districts: The North Kavirondo District, and the Central Kavirondo District. Between them, they comprise an area of over 4,000 square miles, contain about 208,000 huts, and carry a population of over 500,000. In the Central Kavirondo District plague has been endemic for many years, certainly since before 1913, while since 1919 outbreaks have been of frequent occurrence in the North Kavirondo District. In 1919 the number of

deaths from plague in the North Kavirondo District was estimated at between 1,500 and 2,000, and in 1920 at about 1,000.

The population consists of somewhat primitive Africans, living in round huts with mud walls and grass roofs. The staple food of the people is grain, and this is stored by the natives in small grass-roofed granaries in close proximity to their own huts. Conditions, from the point of view of the domestic rodents, are ideal. From observations which have been made from time to time, it would appear that the average rat population of each hut is about 15, and on occasion as many as 60 rats have been killed in one hut.

Plague prevention under such circumstances is obviously not an easy matter, and previous to 1921 the only method which had been adopted on a large scale was vaccination of the community with Haffkine's prophylactic. Such a procedure, however, besides being both laborious and expensive, is unsatisfactory in that while it may protect the human population for a time, the rat population is unaffected and it is necessary to vaccinate the population again as soon as another epidemic occurs. Further, as has been recounted above, the dangerous black rat was extending his domain and it was desirable, if possible, to limit that extension. Something more radical than vaccination was required.

The institution of a rat campaign on a large scale in British East Africa was first suggested by Prof. W. J. Simpson who, in his "Report on Sanitary Matters in East Africa,"* makes the following statement:

> A similar campaign should be inaugurated against rats to the one recently waged with success in an infected district in Muanza, where, in 1913, 500 persons died of plague. Two Medical Officers, Drs. Manteuffel and Klein, visited the villages and informed the chiefs, elders and villagers that they intended to begin a destructive campaign against the rats, and that they must help them. The proposal was met with opposition at first on the part of the natives, until the doctors explained to them that the rats were enemies to them, not only because they caused plague among them, but also destroyed their crops. The latter reason appealed to the villagers, and they promised to help the doctors and their staff.

* "African," No. 1025.

One cent was to be paid for each rat delivered. The doctors set up their camps several miles distant from each other, and a trained boy and askari with cart visited the villages between. A certain number of the villagers were then deputed to do the work, which consisted in uprooting and burning the scrub around the hut, and in thoroughly beating the roof and sides of the hut with sticks, inside and outside of the hut, to drive out the rats and then kill them, and a ring of men outside to kill any rats that escaped. One cent was paid for every tail and the feet of a rat brought in. The boy and askari had to return with the tails and feet every night, as well as with a number of rats for examination. When this area was completed the doctors moved their camps to another district and proceeded on the same lines. In 10 weeks 1,100,000 rats were destroyed. Out of these 10,000 rats were examined, and of these 4 per cent were found infected. The rats were dipped in disinfectants immediately after they were killed in the village.

A campaign of this kind should begin at the periphery, at the northern side of Yala, for instance, so that infected rats may not be driven into healthy areas.

That is to say, it was suggested that an average of over 15,000 rats should be accounted for per day over a considerable period. It was not easy to see how that could be done. Previous experience of rat-catching, or of securing the destruction of rats by the offer of a reward, had so far only been attempted in the towns, and the results had been most discouraging. Of the prospects in the native reserves, nothing was known. The matter was, however, discussed with the District Commissioner of North Kavirondo, and early in April, 1921, it was decided to make an experiment.

A few days later, therefore, at the conclusion of a large meeting of natives in the location of South Kitosh, in Kavirondo, after a recital of the old and well-known story of the connection between rats and plague, and the destruction caused by the former to grain and crops, it was suggested that the time had come when they should take some action in the matter. The District Commissioner then informed the meeting that he would return in 4 days, that in the interval every one should endeavour to catch as many rats as possible, and that on the 4th day they should meet him again in the same place, bringing with them all rats which they had destroyed. The proposal was received with a certain

amount of amusement, and it was not easy to be sure whether it was appreciated that the suggestion had been put forward in all seriousness. One would not have been surprised if on the day arranged no rats had been produced.

The result was, however, successful beyond expectation. Upon our returning 4 days later, men, women and children were found streaming into the meeting place from all directions. All were carrying rats. Some brought only a few, some brought baskets full. In all, 5,697 were counted, and when we left, more were still arriving.

Thereafter the experiment was repeated in the other locations of the district, and at the same time an attempt was made to organise a campaign, by instructing the chiefs to tell the people to bring in rats to the native courts, which are held weekly on Mondays in each location. It was soon obvious, however, that such an arrangement would not be satisfactory, for a number of reasons: — firstly, no native likes carrying dead rats; secondly, they particularly objected to transporting for some distance, on Mondays, rats killed at any time during the previous week; thirdly, it was not possible entirely to rely on the enumeration; and lastly, it was soon obvious that, if the matter was to be left solely to the chiefs, it was not likely to be prosecuted with vigour for any length of time.

It was therefore ultimately decided to instruct the people, through their chiefs, that they should destroy rats on every opportunity, that they should cut off the tails and burn or bury the bodies, and that from time to time the bundles of tails were to be delivered to their chiefs. The chiefs were to send all bundles so collected to the District Commissioner, at the end of each month, and they were told that an average number of 5 tails per hut, per month, should, if possible, be maintained. At the district headquarters, the tails are in all cases counted, and the number verified by a European, usually the Medical Officer. If the number sent in by any chief is less than his location might reasonably be expected to yield, he is informed to that effect, and told that his people must do better next month, and if possible, his location is visited towards the end of the next month by the Medical Officer, to ensure that these instructions are being carried out. This, in brief, is the system now in vogue, and it has proved entirely satisfactory in practice.

Certain details with regard to the execution of the campaign are, however, of considerable importance, and require elaboration.

It is to be noted that no rewards are given. Firstly, because it would have been impossible to continue a system of rewards for any length of time if the results had been at all successful. The work has been done by the people themselves, under the direction of the ordinary administrative and medical staff of the district. Secondly, if rewards had been offered, the campaign would have finished when the funds became exhausted. Thirdly, it was desired that the work should be done intelligently; that the people should destroy rats because it was a wise and useful thing to do, and not merely because the Government, for some reason which the native could not understand, was sufficiently foolish to be willing to pay for tails. It was desired, if possible, to make rat-destruction a habit and part of the civilisation of the people.

To some extent this has been accomplished. In the old days little notice was taken of the rat; now, if he is seen or heard, he is hunted, and large numbers of tails are willingly sent in as a routine, without either administrative or Medical Officers having to take much trouble in the matter.

It is to be noted that only tails are asked for, and that the people are told to burn or bury the carcases. This method of procedure has sometimes been deprecated as being dangerous, because the carcases may be neither buried nor burned, but may merely be thrown into the nearest bush or long grass, where their fleas may leave them and attach themselves to other rodents or to man, and, if they be infected, so spread the disease. Possibly this may occasionally occur, as it is very doubtful whether many natives take the trouble either to bury or burn the carcases, but it is not easy to see how such a possibility can be avoided without making the execution of the campaign too laborious.

To enforce the carriage of all the carcases to one central point, where they could be buried or dipped in disinfectants, would be to incur the much greater risk of carrying fleas from an infected area to an uninfected area, since we are dealing with a large district, and it is not possible always to know the exact points at which rat plague exists. The problem is a large one, and can be attacked only by means of an exten-

sive and continuous campaign. No campaign will be continuous if it be made too laborious, and it is undoubtedly laborious to carry rat carcases every day to a depot. One object is to keep the population of domestic rats at a low figure over as large an area as possible, and if that be done it is of relatively little importance if a few inflected fleas escape.

To have a large number of carcases brought to one place, on one day, is useful for purposes of advertisement at the commencement of a campaign, but it is not a method which can or should be maintained.

The last point of importance is that the reasons for the campaign must be made plain to the natives. To tell them once, is not enough. The story of the rat and the flea and plague must be told again and again, by both medical and administrative officers whenever an opportunity presents itself, and the role of the rat in the destruction of stored grain should not be forgotten. This is constantly done in both the Kavirondo districts and, in addition, it is explained why for the present the people's energies are to be concentrated on the destruction of the domestic species only. If this be not done, a number of the lazier or less intelligent natives will take no action themselves, but will turn the matter over to the children. The latter will, as a rule, be unable to catch the elusive and well-sheltered house rat, and will concentrate their energies only on the field species, whose destruction in considerable numbers is fairly easy. Whether or not, as a result of such lectures, the results so far have been very satisfactory in this respect, an examination of the tails sent in, showing that on an average over 90 per cent of the rats destroyed have been of the domestic variety, would seem to be a conclusive answer.

Differentiation of the dried tails of the domestic rats from those of the field rats is not difficult, and whenever any undue preponderance of the latter is noticed in a catch, the chief should be informed that his people are not giving sufficient attention to their huts.

The campaign has now been in operation for nearly 3 years, and tables showing the number of rats destroyed for each location of the 2 districts of Central and North Kavirondo, in 1921, are here shown.

TABLE 1

Rat Destruction Return:—North Kavirondo District, 1921

Location	Chief	Huts	April to June		July		August		September		October		November		December		Total	
			No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut
Wanga	Mumia	7,749		—	—	—	9,069	1.1	4,230	.5	6,338	0.81	11,198	1.4	5,944	0.7	36,779	4.7
Marama	Malama	8,694		—	—	—	27,363	3.1	—	—	10,923	1.25	30,558	3.5	64,313	7.6	133,157	15.3
E. Kakamega	Osere	2,830		—	5,180	1.8	3,064	1.0	—	—	7,237	2.55	10,094	3.5	14,935	5.2	40,510	14.3
Watsotose	Wambani	1,711		—	—	—	—	—	537	.09	72	—	6,751	3.9	5,229	8.9	22,589	13.2
W. Kakamega	Mulimo	5,432		—	2	—	1,388	.2	339	.06	7,043	1.29	23,998	4.4	26,418	4.6	59,188	10.9
Mukulu	Repande	1,643		—	—	—	—	—	—	—	3,295	2.00	2,060	1.4	7,806	4.7	13,161	8.01
Kakalewa	Ndombi	1,782		—	—	—	—	—	426	.2	1,429	0.8	6,529	3.6	7,499	4.2	15,883	8.9
Kabaras	Mwanza	3,037		—	—	—	—	—	—	—	18,923	6.23	5,130	1.6	5,775	1.9	29,828	9.8
N. Kitosh	Marunga	8,505		—	—	—	—	—	—	—	6,942	0.8	40,769	4.7	25,718	3.02	73,429	8.6
S. Kitosh	Sudi	7,017	95,429	—	—	—	—	—	—	—	39,804	5.6	46,139	6.5	16,838	2.3	102,781	14.6
Wamia	Kadakada	6,261		—	26,500	4.2	—	—	—	—	5,929	0.9	36,796	5.5	4,300	0.6	73,525	11.7
Marach	Oduya	5,107		—	—	—	—	—	—	—	5,286	1.1	12,662	2.7	12,780	2.7	30,728	6.01
Ohaye	Okwara	4,447		—	35,811	8	—	—	—	—	11,154	2.5	24,669	5.5	9,719	2.1	81,353	18.3
Kisa	Kuta	1,725		—	4,300	2.4	6,175	3.5	996	.5	—	—	6,225	3.6	5,440	3.1	23,136	13.4
Tiriki	Amian	4,986		—	3,300	.6	225	0.4	1	—	2,557	0.5	23,642	4.7	28,028	5.6	57,753	11.7
S. Maragoli	M'nubi	6,853		—	11,500	1.6	36,858	5.3	—	—	—	—	22,278	3.7	36,246	5.5	106,882	15.4
N. Maragoli	Shwachi	9,232		—	4,500	.4	6,175	—	—	—	19,645	2.1	13,601	1.4	34,400	3.6	78,321	8.4
Bunyere	Songoro	9,484		—	5,600	.5	5,993	.6	—	—	691	0.07	32,108	3.3	47,019	4.9	91,411	9.6
Waholo	Were	2,470		—	—	—	—	—	23	—	4,922	1.9	3,400	1.3	6,945	2.8	15,290	6.1
—	—	—		—	—	—	—	—	—	—	—	—	—	—	—	—	95,429	.9
Total	—	98,965	95,429	—	96,693	—	96,310	—	6,552	—	152,190	—	358,607	—	375,352	—	1,181,133	11.9

TABLE II

Rat Destruction Return:—Kisumu and Central Kavirondo Districts, 1921

Location	Chief	Huts	JULY		AUGUST		SEPTEMBER		OCTOBER		NOVEMBER		DECEMBER		TOTALS	
			No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut	No. of Rats	No. per Hut
Alego	Ngonga	13,169	11,901	.9	—	—	19,865	1.5	17,600	1.3	7,000	.5	42,939	3.3	99,305	7.5
Asembo	Odindo	5,465	14,744	2.7	6,964	1.3	9,330	1.7	9,073	1.1	10,884	2.0	18,800	3.5	59,795	10.9
N. Gem	Ogada	10,162	17,129	1.6	—	—	52,024	5.1	25,347	2.5	20,060	2.0	61,790	6.1	176,350	17.4
S. Gem	Ndeda	6,164	24,899	4.0	3,296	.5	10,335	1.7	7,630	1.2	9,715	1.6	15,010	2.4	70,885	11.5
Kadimu	Okello	2,259	2,940	1.3	3,787	1.7	6,366	2.8	—	—	8,366	3.7	6,950	3.1	28,409	12.6
Kajulu	Owuor	2,638	1,490	.5	1,615	.6	6,193	2.4	540	.2	10,848	4.1	4,515	1.7	25,201	9.6
Kano	Amimo	14,880	4,240	.3	3,840	.3	1,365	.1	15,580	1.0	23,163	1.6	14,900	1.0	63,088	4.2
Kisumu	Obiero	5,578	6,380	1.1	—	—	7,682	1.4	940	.2	4,060	.7	3,290	.5	22,352	4.0
Nyakach	Kere	7,741	—	—	460	.1	7,056	.9	4,749	.6	1,730	.2	3,300	.4	17,295	2.2
Nyangori	Sonono	2,270	1,093	.4	—	—	1,190	.5	590	.2	5,050	2.2	4,383	1.9	12,306	5.4
Sagam	Orawa	1,873	9,740	5.2	1,680	.8	7,696	4.1	1,990	1.1	3,349	1.7	1,290	.7	25,745	13.7
Sakwa	Olulu	4,635	8,975	1.9	863	.2	7,105	1.5	480	.1	1,981	.4	1,550	.3	20,954	4.5
Samia	Kadima	8,992	52,000	5.8	20,312	2.2	39,902	4.4	—	—	9,780	1.1	29,174	3.2	151,168	16.8
Seme	Oguk	10,148	8,227	.8	9,810	.9	3,417	.3	5,646	.6	14,780	1.4	5,533	.5	47,413	4.7
N. Ugenya	Muganda	7,460	18,374	2.5	—	—	13,164	1.8	10,832	1.4	6,180	.8	13,935	1.9	62,485	8.4
S. Ugenya	Mugenya	1,913	9,713	5.1	7,600	4.0	1,426	.8	15,632	8.2	3,090	1.6	7,466	3.9	44,927	23.5
Uyoma	Mogi	4,181	2,560	.6	6,730	1.6	10,170	2.4	14,321	3.4	10,718	2.6	1,130	.3	45,629	10.9
Totals	—	109,528	194,405	1.8	66,957	0.6	204,236	1.9	130,950	1.2	150,754	1.4	236,035	2.2	983,387	9.0
Setted Areas	—	—	535	—	3,446	—	4,068	—	484	—	43	—	57	—	8,633	—
TOTALS	—	109,528	194,940	—	70,403	—	208,354	—	131,434	—	150,797	—	236,092	—	992,020	—

In all cases the figures given are those of the number of tails actually sent in, and counted under the direct supervision of an European officer. No rewards were given for rat-destruction, and though in certain locations there was at times a certain amount of slackness, no great difficulty was experienced in obtaining the amount of destruction shown in these tables.

For the present, the figures given are of interest chiefly as indicating that under the circumstances which obtain in these districts, it has been possible to maintain a rat-destruction campaign on a relatively large scale over a considerable period. That the campaign was maintained without payment or reward, and without the engagement of special staff, is a fact which is not without interest, and which will perhaps be the more fully appreciated if it be noted that, had even so small a reward as 2 cents of a shilling been given for each rat caught, the year's catch for 1922 would have involved Government in an expenditure of over £3,500, while, if 3d. a rat (the reward offered in some other countries) had been given, the amount expended would have been over £44,000.

Effects of Rat Campaign on the Incidence of Plague

In the absence of detailed records of past outbreaks of plague in these districts, and particularly in the absence of information with regard to their seasonal incidence, it is not possible to draw any conclusions as to the results of the campaign. It is unlikely that it will be possible to do so until the campaign has been in operation for some years, and though one might be tempted to correlate the small incidence of plague in 1922, as compared with the very considerable incidence in 1921, with the amount of rat-destruction which has been carried out, there is not, as yet, any justification for so doing. That such outbreaks as occurred in 1922 were comparatively few in number, and that none of them assumed any considerable proportions, may, of course, have been due to the campaign. Of that, however, there is as yet no proof. The important point which emerges is that, in spite of the campaign, certain small outbreaks of human plague did occur, *i.e.*, it has been proved that, in spite of the amount of rat-destruction which took place, the infection still persists either in the domestic rodents or elsewhere.

In view of that fact, it is possibly desirable to review the work which has been done, and to consider now whether the campaign is being waged in such a fashion as may ultimately result in the achievement of the ends we have in view.

THE ENDS IN VIEW

These are three in number:

1. It is hoped so to train the people, as communities, in the destruction of rats that they will be in a position, under proper direction, to prevent any outbreaks of plague that may occur from attaining serious proportions.

2. It is hoped to teach the individual that the prevention of the disease in his own hut or boma lies in his own hands, and to convince him that it is worth his while always to be taking the steps necessary for such prevention.

3. It is hoped that by intensive killing over a period of years either (*a*) all infected rats may be killed off, or (*b*) the rat population may be kept so low that all infected rats shall have an opportunity of dying off without propagating the infection and that, following either or both of the above results, the infection may disappear from these districts. The achievement of this end is, of course, dependent on the infection's being confined, in these areas, to domestic rodents alone.

The first of the above ends has probably been achieved in at least a few locations. The second has possibly been achieved in the case of a few individuals. More cannot be said, nor is it likely that much more will be possible till the natives of Africa come to put a higher value in their own potentialities than they do today. The third end in view — the elimination of the infection from the districts — has not so far been accomplished, and it is in consideration of this fact that it is particularly desirable to review the work which has been done, and to ascertain, if possible, the effect which the campaign is having on the rat population.

THE EFFECT OF THE CAMPAIGN IN THE RAT POPULATION

With the object of ascertaining the effect of the campaign on the rat population, a comparative analysis of the returns of destruction in 1921 and 1922 has been made, and is given in Table 3.

TABLE III

North and Central Kavirondo Districts

COMPARATIVE ANALYSIS OF RAT DESTRUCTION RETURNS FOR 1921 AND 1922

	Year	Total no. of rats destroyed	Average no. of rats destroyed per hut for all locations		No. of times the Standard Figure of 5 rats per hut per month was attained or exceeded			Largest average figure per hut for any location for any one month	No. of locations in which the figure of 10 rats per hut per 6 mos., or 20 rats per hut per year was attained or exceeded	Largest average number of rats per hut; (*a*) per 6 mos., or (*b*) per year for any one location
			Per 6 mos.	Per yr.	Once in a location	Twice in a location	Three times in a location			
Central Kavirondo District.	(1) 1921. 6 months only	983,387	9	18	6 times	Twice	..	8.2 rats	7	(*a*) 23.5 (or 47 per year).
	(2) 1922. 12 months	1,456,586	..	13.3	5 times	Once	..	8.4 rats	4	(*b*) 35.5
	(3) Total for 18 months	2,439,973	..	..	11 times	3 times	..	8.4 rats	..	..
North Kavirondo District.	(4) 1921. 9 months only	1,181,133	10.9	21.9	12 times	Twice	..	8.9 rats	10	(*a*) 18.3 (or 36.6 per year).
	6 months only	1,085,704	..	..	..	..	..	..	..	..
	(5) 1922. 12 months	2,118,616	..	21.5	11 times	Once	Once	7.3 rats	10	(*b*) 29.4
	Total for 21 months	3,299,749	..	..	23 times	3 times	Once	8.9 rats	..	..
Total for 1922, both districts (lines 2 and 5)		3,575,202	..	17.1	16 times	Twice	Once	8.4 rats	14	35.5 (per year).

Number of huts in North Kavirondo, 98,965.
Number of huts in Central Kavirondo, 109,528.
The estimated population of North Kavirondo is 295,846.
The estimated population of Central Kavirondo is 275,140.

The average number of rats destroyed per head of the estimated population during the year 1922 was 6.

Note a "Location" is a territorial division of a "District." Each Location is under the control of a Chief, and may contain anything from 1,600 to 14,000 huts. On an average, each contains about 5,000 huts.

In considering this table, a few facts with regard to these districts must be borne in mind: —

	Area Sq. Miles.	Population	Number of Huts
North Kavirondo	2,669	295,846	98,965
Central Kavirondo	1,483	275,140	109,528
Total.....	4,152	570,986	208,493

The huts are in all cases wattle and daub structures, thatched with grass.

Grain in considerable quantities is stored near every hut. The average rat population per hut in another part of the country, where conditions are not unsimilar, in 1921 was found to be 15 rats per hut for 180 huts examined.

The problem of carrying out rat-destruction on a large scale over an area of 4,152 square miles, is obviously one of considerable difficulty. The question arises: Is the rat population being kept at a lower figure than was formerly the case? A direct experiment is difficult to devise as the rat population of the district probably varies considerably, not only from time to time, but from area to area. At first glance, the results recorded in Tables 1 and 2 seem reassuring while the analysis given in Table 3 shows that, on the whole, destruction for the 12 months of 1922 was less, proportionately, than for the last 6 months of 1921. This falling off might, however, be due entirely either to one or other of the following causes, or to some or all of them.

1. To there having been a falling off in the vigour with which the campaign was prosecuted.
2. To the rats having become more wary, or to an alteration having taken place either in their habits or their habitat.
3. To there having been a reduction in the rat population consequent to the destruction carried out in the last 6 months of 1921.

It is possible that the first of these causes has operated to some extent, if for no other reason than because the novelty had worn off. On the other hand, organization has improved and the people have developed the technique of rat-catching, while the use of a native trap of their own devising,

and of remarkable efficiency, has become fairly general throughout a number of the locations.

That the second cause has operated there is no evidence.

Against the third factor having yet come into play, there is a considerable amount of evidence. The rat population may be considerably less than was formerly the case, but it would not appear that any falling off in the number of rats destroyed can possibly be accounted for by there being fewer rats available.

The largest number of rats killed per hut, per six months, in any location of either district, for the period July to December, 1921, was 23.5 — the figure reached in the South Ugenya location of Central Kavirondo — as against the average figure of 9.9 rats per hut over all the locations in the district, over the same period. For the 12 months, January to December, 1922, the highest figure per hut was 35.5 — again in South Ugenya — while the average over all locations was 17.1.

By 6 monthly periods the figures for South Ugenya are as follows: —

Location of South Ugenya

Period	Number of Rats Killed	Number of Rats per Hut, per 6 Months	
July to Dec. 1921	44,927	23.5	
Jan. to July 1922	43,405	22.6	—35.5 per year
July to Dec. 1922	24,553	12.8	

There are no notable differences between the location of South Ugenya and the rest of the district, and no reason is apparent why more rats should have been killed there than elsewhere, save that the chief of that location is a native of unusual intelligence and energy. Had the inhabitants of all the locations of both districts been as active as those of South Ugenya and killed rats to the extent of 35.5 per hut, per year, the total rat-killing for the year should have been 7,387,017. But it was less than half that number, being only 3,575,202.

It would therefore appear that 3,811,815 rats which might have been killed, were left alive, and 3,811,815 rats for the whole of the 2 districts equals 18 rats per hut, or more than

the estimated normal rat population at any one time. Doubtless many of these 3,811,815 rats must have met a natural death during the year, but many also must have survived and produced offspring. Whatever, therefore, may have happened in South Ugenya — and it is possible that there the falling off in the 3rd 6-monthly period was due to lack of rats to kill — it would appear that this cannot have been the case in the districts generally, and that, so far as reducing the level of the rat population is concerned, the campaign has probably been without effect.

It would, therefore, seem that we are not yet killing enough rats appreciably to affect their numbers, which would appear to continue to be effectually limited chiefly by the available shelter and food supply. All that we are doing is to run through the generations a little quicker. In so doing, we may be accomplishing two things: —

1. We may be eliminating the infected rats, or
2. We may be eliminating an immune generation of rats.

If the first be accomplished, the second is of little importance; if the first be not accomplished, we might be in a worse position than before the campaign started, were it not for the fact that the people are now in a better position to carry out, at short notice, an exceedingly intensive local campaign whenever they may be required to do so.

United Fruit Company Hospital at Preston, Cuba

THE ECONOMIC VALUE OF A HOOKWORM CAMPAIGN*

B. E. Washburn, M.D.

Economic results in public-health work are always impressive, since they provide a means for estimating the value a community derives from expenditures for disease-prevention. The success of the Jamaica Hookworm Commission during the past five years has been due largely to the fact that its campaigns have produced results of marked economic value, from the standpoint of the community, from the standpoint of the employer of labor, and from the standpoint of the individual. Furthermore, these campaigns may be regarded as being typical of what can be accomplished in any community in the tropical or the temperate zone, by making relief work against hookworm disease the basis of an active educational campaign in preventive medicine. Especially they teach the role that sanitation plays in disease-prevention. In Jamaica, the main object of every hookworm campaign has been to teach the people the value and the necessity of sanitation; treatment for hookworm disease has been used as a demonstration of the remarkable benefits that can be derived from soil-pollution control.

The plan is to select, in thickly populated communities, definite areas that have been completely sanitated in advance of the campaign. The latest methods of examination and treatment are employed in such areas in such a way as to produce the greatest educational results. The idea is to make the demonstration campaign thorough and impressive so as to reach the entire Colony and interest all the people in sanitation.

As evidence of the success of these hookworm campaigns it may be stated that:

Of a population of more than 60,000 people in the demonstration areas, more than 99% coöperated, and were examined for hookworm disease.

* The work reported in this paper was conducted under the joint auspices of the International Health Board of the Rockefeller Foundation and the Government of Jamaica.

That more than half of the 14 parochial boards of the Island are advocating sanitation, and are enforcing the installation of sanitary latrines.

That 3 parishes at present have full-time medical officers of health, while others are considering the employment of such officers in order to give a more rapid extension to their public health work.

That there has been created a favorable sentiment for sanitary control by Government, as well as a widespread desire for public-health education and an increased activity in disease control and prevention.

The increase in knowledge of disease-prevention, on the part of the people, is an outstanding feature in the history of Jamaica since the World War. Public-health propaganda has been carried on by the Government, through its Central Board of Health, agricultural societies, schools, and other agencies. The part played by the Hookworm Commission, in this movement of public health education, has been to demonstrate: (1) that definite results follow organized control of soil-pollution, and (2) that disease-prevention has a monetary value.

ECONOMIC VALUES OF A HOOKWORM CAMPAIGN FROM THE STANDPOINT OF THE COMMUNITY

1. A hookworm campaign was conducted in the Vere Area of lower Clarendon Parish, during 1920. In the preceding year (1919) the average daily number of patients treated in the Government Hospital of the Area was 78, and the average for the 5 years from 1915 to 1919, was about the same number. During 1920, following the campaign, the average daily number of patients dropped to 72; during 1921, to 57; during 1922, to 52; and for 1923 the daily average was only 45. (See Chart No. 1).

As would be expected, this large reduction in the average daily number of patients has caused a similar reduction in the number of beds provided, according to the Government estimates, for the Vere Hospital, — this reduction being from 80 beds in 1920, to 50 beds in 1923. It seems reasonable to assume that the number of beds sanctioned for a district hospital, for any given year, is based on the demand as estimated from the needs of the previous year. The average

annual cost per bed, in the Vere Hospital, was £27. 12. 0 in 1919 and £38. 3. 6. in 1923. The increase in cost per bed, in 1923, above the cost per bed in 1919, makes it difficult to

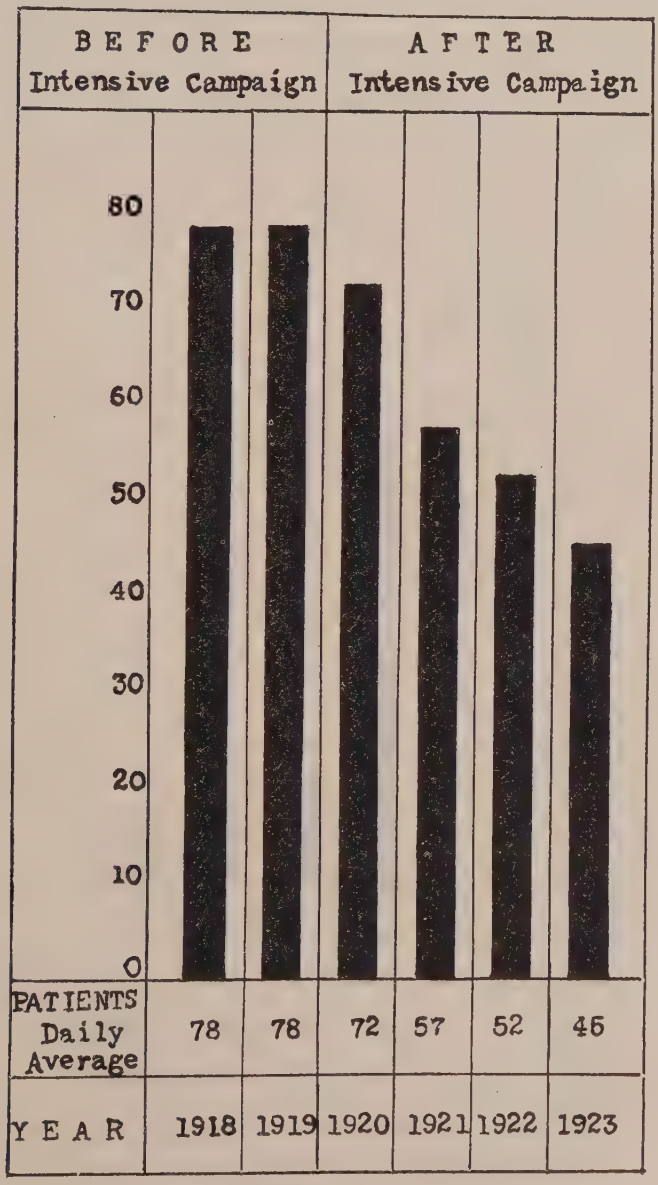


CHART NO. I.

estimate the saving to the Colony from this reduction in the number of hospital beds. But, based on the cost per hospital bed for 1923, this annual saving in the Vere Hospital

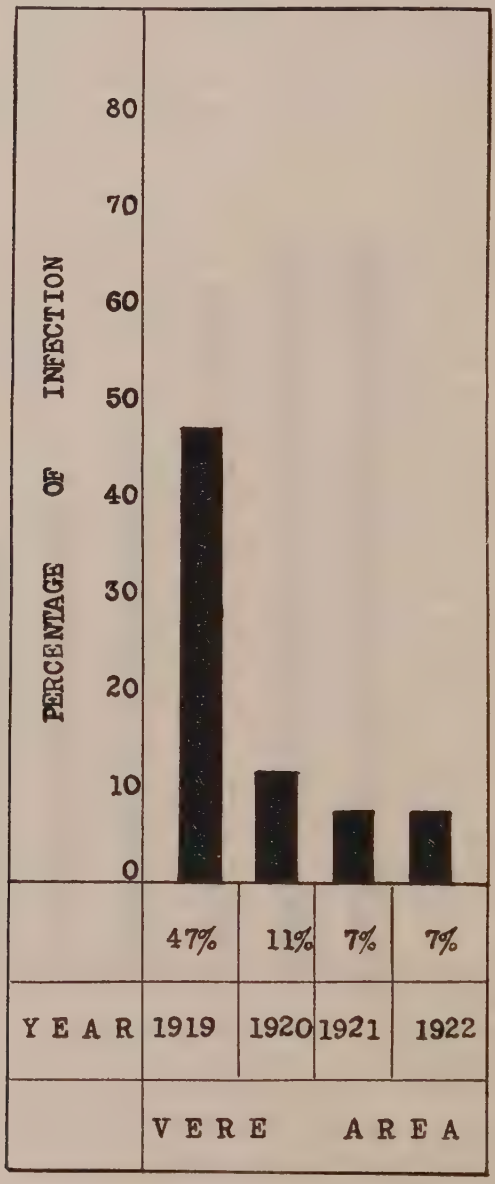


CHART NO. II.

amounts to 30 beds at £38. 3. 6. per bed, or a total of more than £1100 for a year.

2. The examination of the people living in the Vere area for hookworm infection, was carried out in November and December, 1919. Re-examinations were made during December, 1920, and during 1921 and 1922. The percentage of infection found upon the first examination, in 1919, was 48%; in 1920 it was 11%; in 1921 it was 7%; and in 1922 it was only 6%. (See Chart No. 2.) It should be stated that after the treatment campaign in Vere, as has been the case in all the demonstration areas, the Parochial Board placed permanent sanitary inspectors in the area, to maintain the system of sanitation installed previous to the treatment campaign. The relation between the percentage of hookworm infection and the number of cases treated in the hospital in the Vere Area, is further shown by the report, in 1921, of Dr. M. T. Cassidy, who was then the district medical officer for Vere. Dr. Cassidy reports that up to 1920 more than 80% of the patients admitted to the hospital were found to be infected with hookworms; and that in many instances this infection was the underlying cause of the patient's illness; but that during 1921 not more than 5% of the patients admitted to the hospital showed signs of hookworm infection.

3. The hookworm campaign was conducted in Spanish Town, from October 1920 to the end of 1921. Spanish Town — the site of the Government Hospital, which serves the town and the surrounding districts — has a combined population of about 18,000. During 1919, 76 cases of typhoid fever were treated at the Spanish Town Hospital; during 1920 there were 73; during 1921 there were only 53 such cases; in 1922 only 29; and in 1923 there were only 6 cases. As regards dysentery, the reduction in the number of cases was even more marked. In 1920, 30 cases of dysentery were treated in the hospital; in 1921, only 5; in 1922, 2 cases; and in 1923 there was only 1 case. (See Chart No. 3.)

The average daily cost per patient in the Spanish Town Hospital from 1920 to 1923, was about 2/–. Typhoid patients require special diet and nursing, but the increased cost for this particular class of patients could not be obtained. If, however, the cost is estimated on the basis of the average

2/– per day, assuming that each typhoid patient remained under treatment for 6 weeks, the cost reduction for this one hospital for typhoid alone, amounts to about £300 per year.

In the Richmond Area of St. Mary Parish, where the hookworm campaign is now operating, by the present methods of constructing sanitation, the total cost to the Parochial Board for a population of 20,000 people was less than £500. A comparison of this cost of sanitation with the reduction in hospital costs in the Vere and Spanish Town Areas, clearly

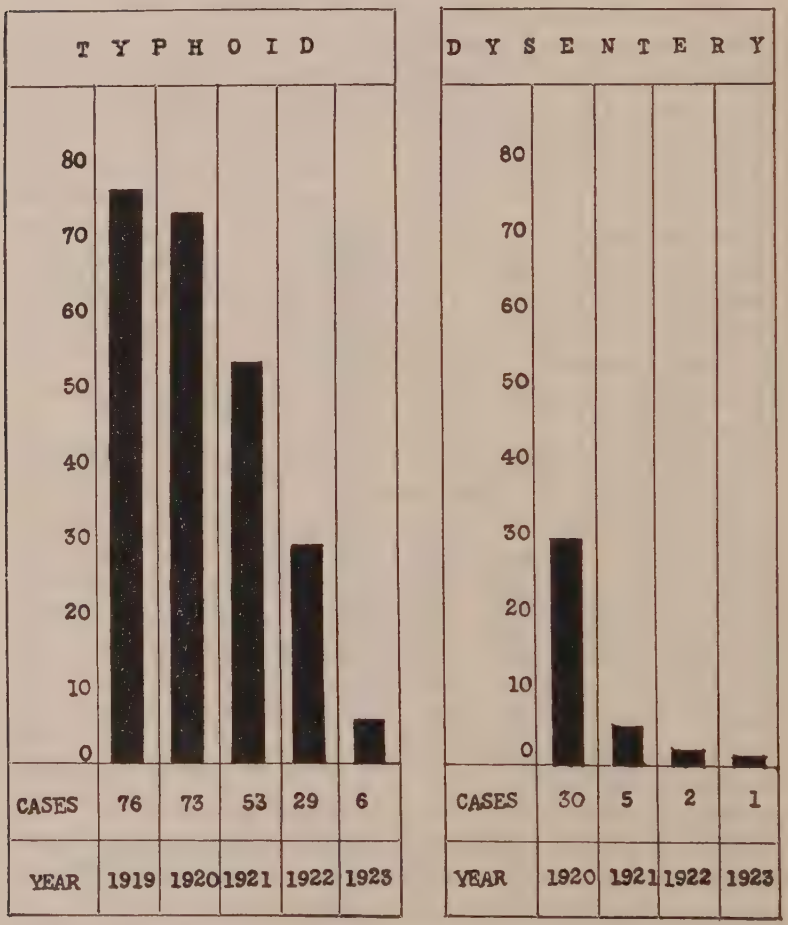


CHART NO III.

shows the economic possibilities of a hookworm campaign with its attendant sanitation.

4. It has been demonstrated by the campaigns of the Jamaica Hookworm Commission that the amount of sickness from all diseases, but especially from typhoid fever and dysentery, is decreased as a result of a hookworm campaign.

Economic Values of a Hookworm Campaign from the Standpoint of the Employer of Labor

A marked reduction in hospital cases, especially in the cases of bowel diseases, indicates improvement in the general health of the people in the districts included in hookworm campaigns. The economic results of this improvement can be measured in the effects produced on estate laborers.

During 1921 and 1922 the Hookworm Commission conducted campaigns on the estates of the United Fruit Company, in the Parish of St. Catherine. In May, 1924, a questionnaire asking for reports as to the results of these hookworm campaigns, was sent to the seven managers of the Company's estates groups. Five questions were asked, and representative replies from the seven group-managers follow:

Question I: *Are the people healthier, and can they do more satisfactory work, than before the campaign?*

All seven managers were emphatic in their statements that the laborers are healthier and can do more satisfactory work. For example, the manager of Cumberland Pen Estates says:

> The hookworm campaign, as I can see from comparison with former records, has produced a marvelous change among the laborers. They are healthier and capable of performing harder work, thereby giving greater satisfaction than previously.

The manager of the Watson Grove Estates replied:

> In my opinion, the laborers are much healthier and are doing more satisfactory work since treated for hookworm disease.

Question II: *Have the laborers been able to give more regular service than before they were treated for hookworm disease? What was the average amount of work done, per week, by each laborer before treatment? After treatment?*

Five of the seven managers replied that their laborers have given more regular service since being treated for hookworm disease.

The manager of Government Park Estate says, "The average working time is increased 25% after treatment." Watson Grove records showed an average of 2½ days per week, per laborer, before treatment — and 5 days after treatment. Bushy Park Estate reports an increase of one day per week as the average. Cumberland Pen reports the average week's work as being three days, before treatment — and a full week afterward. The records from Congreve Park were 3¾ days before, and 4¾ days after, treatment. In districts where crop seasons are short, and where there is emergency work, the value of an increase in the average amount of work done per week is apparent.

Question III: *Have the following complaints among the laborers been decreased since the campaign: — Typhoid, Malaria, Bad Colds and Fever, Dysentery, and Bowel Troubles?*

All seven reports testify to marked decreases in all these diseases.

Question IV: *Do you find any difficulty in getting the laborers to use the places of convenience on the estate?*

The replies from all seven managers indicate that the laborers use the sanitary conveniences. The tone of the replies is shown in the two following reports: "Not when the sanitary conveniences are within easy distance." "At first there was some difficulty in getting the laborers, and especially the children, to use the sanitary conveniences. At present they all use them readily and give no trouble."

This same questionnaire was sent to all the leading estates in the Parishes of Clarendon and St. Catherine, where hookworm campaigns had been conducted. The replies received are all similar to those coming from the United Fruit Company Estates, so I will not refer to them in detail.

The results of the hookworm campaign from the standpoint of the employer of labor, are described as follows by Mr. H. B. Walcott, Manager of the Amity Hall Estates during 1920 and 1921, in a report made to the Clarendon Parochial Board:

> Many individual laborers have had their health improved, and this has resulted in their ability to do more regular work. Formerly there was a great deal of time lost from sickness, but since the hookworm campaign, it is rare to find a laborer who is unable to give full time. This is the most important economic

factor resulting from the campaign. Since the barracks have been sanitated, there has been no typhoid, and dysentery is rare.

Economic Values of a Hookworm Campaign from the Standpoint of the Individual

It is well known, and therefore perhaps commonplace to state, that treatment for hookworm disease renders an individual capable of doing a greater amount of more effective work; that the attendant good health results in a monetary saving on medical bills, and in other ways; that children, upon being relieved of hookworm infection, are rendered better able to take advantage of their opportunities for obtaining an education. These factors, of course, are recognized as being of economic value in the life and welfare of the individual. But it is difficult to obtain concrete examples of particular individuals whose actual earnings, as well as their capacity for earning, have been actually increased.

1. The fifth question in the questionnaire sent out to estate managers was as follows:

Question V: *Do you know of any individual laborer who is able to do better work than before he was treated for hookworm disease? Of any one who is able to earn more money?*

A great majority of the answers were in the affirmative, and ranged from general statements to concrete examples, as illustrated by the following replies:

> On several occasions I have conversed with the laborers *re* treatment and effects, and they have all informed me that they are able to do more work, and earn more money if provided with more work; and from personal observation I concur.
>
> A particular case is of one, Thomas Reynolds, who is now earning fully 200% more pay. From a feeble messenger at 5/– per week, he is now assistant in one of our pumping plants, earning 16/– to 18/– per week.
>
> My contractor here is a very hard-working man (did not have hookworms) and unless his assistants work hard, too, he will not keep them. He now has working with him regularly men who were cured of hookworm disease, whom he refused to employ before treatment as they were no good. Naturally, being able to do more work, the laborers earn more money.
>
> There is the case of Adolphus Williams, from Morelands Estate, who formerly was never able to earn more than 12/6 per

week. Since being cured of hookworm disease, he has become a field headman and earns 30/– per week.

The following extract is from a letter sent by the Master of a Parochial Poor House:

> After the hookworm treatment I noticed a great change in the general condition of the inmates, and quite a few have been discharged feeling strong and well, as they expressed a desire to go home and support themselves.

2. The laboring class in Jamaica has been very appreciative of the benefits received through hookworm treatment, and many individuals have written interesting letters expressing their appreciation. Such letters from the people are sincere in tone, and what they record can be taken as representative of benefits to a majority of those who are treated during a hookworm campaign. The following are given just as they were received, even as to spelling and punctuation:

> I Sarah Youngsam was examined and was found with hookworm. I took two treatments and was cured. Before I took the treatments I could not work, now I can go to my work as a field laborer and can do my tasks at 2/6 and 3/– by midday, coming home feeling hearty and strong.

> To the Jamaica Hookworm Campaign, I have five treatments of the hookworm pills and I have been cured at last thank God from that dredful pest. Six of us in my family have been treated and cured. I can tell you doctor every one of us was shameful meagre and horbly crippled, and yet we were fat once. We are all new people now. I am a changed man in every way. Hart stoped to palpetate, giddiness in head ceases, bad feelings all gone, ulcer on foot healed, in fact I can hardly know myself. We are all laborers and we could scarcely earn our living, now we can work harder and with greater ease making more money than usual.
>
> With three cheers we wish you a great name and a happy Christmas. Robert Lewis and Family.

SUMMARY AND CONCLUSIONS

1. The Jamaica Hookworm Commission has conducted campaigns, from an educational standpoint, among the people in seven rural and one urban area of the Colony, receiving the coöperation of over 99% of the people of all

classes. The results of these campaigns demonstrate that a native population in the tropics can be educated in disease-prevention. Such results may be regarded as typical of what can be accomplished through a hookworm campaign in any thickly populated community in the temperate or tropical climate, where there is a moderate amount of hookworm infection, where sanitation is inaugurated in advance of the treatment work, and where education in disease-prevention is made the basis of the campaign.

2. The results of the Jamaica campaigns have been of marked economic value from the standpoint of the community, of the employer of labor, and of the individual.

A marked decrease in the amount of sickness from all diseases, but especially from typhoid fever and dysentery, with the attendant savings in hospital provision, is the most important result from the standpoint of the community.

The improvement in health among laborers, resulting in their ability to do more regular work and to put in full time, is the important factor of economic value from the standpoint of employers of labor.

Better conditions of health, with increased resistance against contagions, and the capacity to do more work and earn more money, are among those results of hookworm treatment which tend to improve the lot of the individual.

3. The economic results of a hookworm campaign should make a strong appeal both to the tax-payer and to the Government, as a means of lessening sickness and diminishing hospital costs; to employers of labor, such campaigns mean more regular, more efficient, and better contented laborers; to the infected individual, hookworm treatment means the removal of a handicap, with consequent ability to earn more money, to better provide for self and family the necessities of life, and to become a better citizen. And decreased sickness, efficient and regular labor, and responsible citizens, are essentials in community advancement.

DISCUSSION

Dr. Bailey K. Ashford (Opening the Discussion). — Dr. Ashford said he had listened to the paper with a great deal of satisfaction, for, he stated, I take pleasure in saying that I am now living in the American Tropics, and I see that Jamaica is being added to the list as another of the Antillan Islands where hookworm-disease

campaigns have been successful. The North American and Central American knowledge of hookworm disease was born in the American Tropics, and it was there, too, that the first fruits of victory over this disease were reaped. In order to understand the economic side of the question in Porto Rico — for that is the only place in which I have worked continuously — it is necessary to know that in 1900 and 1901 we were having a death rate from anemia of 12,000 a year, out of a total of 36,000 deaths from all causes. One-third of the deaths in Porto Rico were attributed to anemia, and certainly the vast majority of these cases were of uncinariasis.

Before we go any further, and in order to understand the importance of this disease in Porto Rico, we must consider this: Uncinariasis in the North reduces labor efficiency and stunts growth. There it is rather subtle in its effect. In Porto Rico we had terrible infections. They ranged, on an average, from 1,000 to 1,500 worms to the patient. The effect of infection was aggravated by the extreme malnutrition of the people. With this food deficiency present, hemolytic poisons work great havoc. This feature distinguishes the Uncinariasis epidemic in Porto Rico from all of those in the Western world, although similar epidemics in the East have been described.

There is another phase of the disease that we should consider, and that is its effect upon the wages of our Porto Rican country laborer. On account of their anemic condition, the people on coffee plantations were receiving a wage of only 30 cents a day, — at par, and generally this wage was below par. That shocked the Northerners. The Porto Rican employers said that they could not pay more, because the laborers were not worth any more, and to pay a higher wage would be economically ruinous.

When I jumped into that work, I felt quite dubious as to how many people we could treat the first year. We treated 5,000, having told the Government that we hoped to treat 500. In the towns we did little "preaching," but we did preach in the country, telling the hookworm victims how the infection occurred. There was no time to rehabilitate the "devastated area." This was frontline work, and we reasoned that every cured person would be one less person to infect the soil.

It was our conviction that the problem of Uncinariasis was not based on considering every foot of land equally infested. It was generally by walking bare-footed into nests of larvae corresponding to an area not much larger than the spot of pollution, that one acquired infection. That was our epidemiological observation.

Now only do we *know* scientifically, by Cort's application of Baerman's method of soil-examination, that this is true. Then we had a death rate of 42 per 1,000; the death rate today is 21 per 1,000. We successfully treated 317,000 out of a total infected population estimated to be 600,000. But to that 317,000 must be added some 200,000 more, who were treated by other physicians and agencies on the Island, not under the same auspices as our work.

When we began in 1904, it fortunately occurred to me to take the hemoglobin of a number of people; so we examined the blood of 549, taken at random as they came for treatment. These hemoglobin estimates were made by the Von Fleischl apparatus. The average hemoglobin of 549 people was 43%. If you stop to think what that means in a working population, you can get a faint idea of the seriousness of Uncinariasis in Porto Rico. At the end of 10 years of work, I naturally repeated these hemoglobin readings in the same country district, and found the average hemoglobin to be 72.2%. That is to say, there had been a gain of more than 60% over the previous figure.

Now comes the most interesting part: I did not care to draw, from my own impressions, conclusions as to the value of this campaign against the disease. I had the scientific facts, and I kept them to myself, but I wrote a letter to 400 planters on the Island, asking for their estimate of results. I received answers from the majority. One question I asked in that letter was:

> What percentage in efficiency for labor have your peons gained, since their treatment for Uncinariasis?

The answers about tallied with the figures showing the rise in hemoglobin, — the composite percentage as shown in the replies, being 67%. After this, wages went up. I submit to you that there is something more than mere coincidence in the fact that you no longer find, in the rural districts of Porto Rico, the sick working class that you used to find. Many people go to Porto Rico today and fail to see much anemia there. When the United States took over Porto Rico, in the year 1900, we found that the export trade, which had begun to improve under military government, was worth $8,500,000. It is, again, something more than a coincidence that this export trade has steadily increased, until this year it is approximately $80,000,000.

I have desired to make a particular point of the early work in Porto Rico, for the Rockefeller Foundation has recently for the first time entered the field there and is doing wonderful work. They understand the situation perfectly well, but I do not know whether the general medical reading public understands it so well. Our work, as I said, was front-line work. The building of latrines

there is to be the permanent defense against hookworm disease. But, although in Porto Rico the disease is now but a shadow of its former self, there is very little difference in the *rate* of infection. You will not find many people sterilized of their Ankylostomes, since the country people in the interior of Porto Rico do not take kindly to the use of latrines. The point is, infections are very much *lighter*.

In those days, all we had to do was to examine the raw feces and make a diagnosis, and we made no diagnosis of Uncinariasis without such a microscopic examination of the feces. Of our patients, 98% were thus found infected. Today, we have the Barber and Lane methods, and others, by which a few eggs are discernible in a large amount of feces, and which reveal very light infections. One must have lived 20 years ago in Porto Rico to know what has been done to reduce this disease. The reduction in infectivity of the soil is believed to be permanent. Conditions might gradually revert to that terrible loss of life and labor efficiency, above cited; but it is not probable nor reasonable to think that such will be the case. The mathematical chances of stepping into an infected spot are much less than before, and when the ultimate death of larvae in the soil — after some months — is considered, new pollution points will be found less heavily infected.

As to the reduction of other feces-borne disease, it is curious that no one in Porto Rico has spoken of this before. Amoebic dysentery is much less frequent than formerly; bacillary dysentery is reputed to have caused severe epidemics years ago, but is not in evidence today; and typhoid fever is far less than it was.

I have been delighted to hear that Jamaica is receiving the same benefits from her campaign against hookworm that we ourselves have received.

Col. James Cran. — Mr. Chairman, I think that in your opening address you made the remark that malaria comes first and hookworm second, in importance of diseases in the Tropics. In British Honduras, I think, we could reverse it. In my opinion, hookworm is more of a detriment than malaria. As a matter of fact, we do not have any very severe infections of malaria, but it is well known that in a certain race, namely, the Maya Indians, there is nearly 100% of hookworm infection. I envy Jamaica the services, for a considerable period of time, of so brilliant a worker as Dr. Washburn. About five or six years ago we enjoyed a short visit from a very able man from the same Institution — namely Dr. Hackett — but it was only a flying visit, in spite of our attempts to persuade him to stay.

We have a difficulty in British Honduras which I think you do

not have in Jamaica; that is, a variety of languages spoken. There are those Indians who speak nothing but the Maya language, known only to themselves; there are a certain number of Spaniards who speak only Spanish; and there are those who speak English. Our great trouble has been to find men to work among the various classes there. We have one, however, who was trained by Dr. Hackett, and who is extremely efficient. This man speaks at least three of the languages. In general, the experience of the workers in British Honduras tallies with the experience recounted by the speakers at this conference. We have done what Dr. Bass recommended, — we have started to educate the young; we have made compulsory in the schools the teaching of the prophylaxis of malaria, dysentery, hookworm, yellow fever, and so on; and we have notified the teachers that at least one question along these lines will be required at the annual examination. The children are teaching the parents the use of the latrines, and the statistics are indicating — as Dr. Washburn has shown — a reduction in the hospital days, due to the reduced morbidity of the disease.

I wish we could persuade the Rockefeller people to come back and give us an overhauling once more, if only that they might see the results of the work that they initiated.

Sir Thomas Oliver. — I should like to state that I am in accord with several of the remarks that Sir James Fowler has made. While I do not feel that from the tropical point of view, I can add anything to the subject of hookworm disease, yet I should like to draw your attention to some of the changes that occur after the malady is carried from the Tropics to temperate zones.

We have no epidemic of hookworm disease on a serious scale in Great Britain, but from time to time, mines have become infected. Under the circumstances, the conditions of life of hookworm larvae are rather different from those of the hookworm under a tropical sun. A few years ago there was an outbreak of hookworm disease in the mines of Cornwall. Its origin was traced to miners who had come from South Africa. The trouble was dealt with as soon as the disease had been diagnosed. The miners exhibited the constitutional symptoms, and also the local effects that develop in the skin, through which the larvae had penetrated.

There was a feeling that the coal mines of Great Britain were not likely to become infected because the temperature is too low; but I carried out a series of experiments in regard to the living conditions of larvae, in order to see what temperature they could stand. I kept larvae in a temperature practically at freezing point for some time; and then, by gradually raising the temperature, I found that the larvae not only lived and recovered, but appeared to be stronger

than those which had not been similarly treated. This circumstance showed that low temperatures in mines cannot reliably be considered an effective safeguard against hookworm disease.

A good deal of miners' disease, also, had occurred in France, Belgium, Germany and Hungary, so I went to those countries and studied it on the spot. At Westphalia I found that several of the mines had been infected; in some of them as many as 75% of the miners had been ill. I do not think that in the temperate zones we find the extreme degrees of emaciation to which Colonel Ashford drew attention. There is a certain degree of emaciation, as well as a great deal of physical disability, which unfits men for work, and in the miners of Germany, Hungary, and Belgium there is a considerable degree of anemia.

As there had been, a few years before my visit, a series of explosions in the coal mines of Germany, due to the great heat of the mines and the accidental firing of coal-dust, the Government passed a resolution that in future the coal mines should be sprayed with water. This precaution stopped the explosions; but a new danger was introduced, — an outbreak of hookworm disease. In going through these coal mines, I found that the wooden props supporting the roofs were extremely wet and pulpy, and that in these props larvae were wonderfully well able to move from one place to another. Experimenting in my own laboratory, if I left larvae in a hollow vessel over night, I found them several inches away from it in the morning. The larvae in the soil of the Ruhr mines were capable of traveling up the wooden props to the extent of two or three feet.

Attention has been drawn by Dr. Washburn and others to the economic value of the treatment of hookworm disease. In Germany, once the disease was detected, the mine-owners and the medical authorities, with their great organizing ability, arranged for and built special hospitals, segregated the patients, and treated them. The iron pails used in the mines for defecation were disinfected every morning, with the result that within a short period there was a considerable reduction in the number of cases in the mines. In addition to the economic value of the knowledge of hookworm disease, there is the humanitarianism aspect of it as well.

When the Mont Ceni tunnel was constructed, there was a considerable death rate among the laborers, and a large mortality among the horses. It was not at first known what was the cause of the anemia from which the miners suffered. The French called it "the malady of tunnel-makers." Dr. Perroncito, of Turin, finally discovered the actual cause of the disease when he found, in the *duodenum*, the Ankylostomata.

A few years later, it was proposed to build, between Brigue in Switzerland and Iselle in Italy, a tunnel now known as the Simplon Tunnel. Before a piece of sod was turned, those who were in charge decided that they would appoint medical men to examine every applicant for work, the stools being especially examined. As a result of this precaution, among all the laborers who worked to construct that tunnel (about fourteen miles long) there was not, I believe, a single death from Ankylostomiasis. I regard this as a great achievement from both a humanitarian and an economic point of view.

Dr. Juan Iturbe. — Dr. Iturbe stated that in 1903 hookworm was discovered in Venezuela. There it was found that almost 90% of the rural population were infected. The first treatment showed favorable results from Thymol. In several cases, the hemoglobin count went up from 60 to 90% in two years. Professor Fülleborn, during his visit to Venezuela, showed me the method used by Baermann, of Sumatra, to discover the Ankylostoma larvae in the soil. This method proved that the majority of coffee plantations and the soil in the vicinity of the houses, were heavily infected with larvae. We cultivated the larvae by Professor Fülleborn's method. To protect the people near their homes, we have resorted to cementing about ten meters around the house.

Dr. Charles Kofoid. — One matter that has been mentioned frequently in the discussion, is the heavy infection in tropical regions, with the more or less well-defined implication that light infections are of no clinical significance. It was my good fortune, during the World War, to have an opportunity to make a study of an area in the United States (in Texas) in which the infection is light. In the 36th Division, at Camp Bowie, the infection among 24,000 men, as a whole, was 12.5% — ranging from a fraction of a per cent to 74% in different companies. During the measles and pneumonia epidemic of the winter of 1917–1918 a study of the incidence of morbidity and mortality in the 36th Division revealed the relation of very light hookworm infection to those two diseases, in general. We found that in men from Texas generally the average number of worms, on treatment, was less than 5, and the maximum record was 300 only.

The statistical analysis of hospital and regimental records of the group with this very light infection, showed a sharp contrast between those with hookworm and those without it. Men with hookworm were 28% more times reported sick, while the number of times they were sent to the hospital was increased 77%. The number of days on sick call in the regiment was increased about 89%; and the death rate due to pneumonia was 90% to 300%

heavier in military units with over 10% hookworm, than it was in units with less than 10%.

In other words, the disease was more frequent, more chronic, and more often fatal, in those who had hookworm than in those in whom it was not found.

Thus, these men who had only a light infection showed marked increase in morbidity and mortality over those who had presumably no hookworm infection.

We also made a study of the intelligence tests of 9,254 men, including two groups containing both literate and illiterate whites and blacks, divided into two groups, *i.e.*, those who had hookworm and those in whom it was not detected. The mental efficiency of infected men showed about 25% average lower rating than those who did not have hookworm. This was true of all the percentile groups, from the uppermost to the lowermost. Therefore, the lower mental efficiency was not the result of heredity or education, but rather was due to the toxic effects of the parasites, even in light infections.

The social aspects of hookworm infection are well illustrated by the following: One of the gold mines in California had a Christian Science Superintendent, who placarded the mine, during the examination of the employees, with propaganda that "germs do not kill." This mine had a dump-hole, used by the men as a latrine, which drained into an adjacent mine. Every man employed on that pump line in contact with the drainage water, had hookworm.

It would seem, from Dr. Washburn's paper, that the elimination or reduction of hookworm in Jamaica tends to increase efficiency and to promote the general well-being of the unfortunate victim. This is good reason for the hope that its complete elimination over large areas, even in the case of very light infections, may do much toward promoting physical welfare and building up the resistance to fatigue and disease. Such results would add greatly to the joy of living, for the individual, the family, and the community.

Dr. Friederich Fülleborn. — We have indeed to congratulate Dr. Washburn on the splendid results he has attained in the fight against hookworm, in Jamaica; and I think no medical man will doubt the great economic importance of such efforts, in relation to so many heavily infected tropical countries.

Colonel Ashford is the man who showed us many years ago that the "tropical anemia" is a consequence, not of the "tropical climate," but of a parasitic disease which we can fight more successfully than almost any other. I think that this fact is never realized vividly enough. Against the "climate" we are helpless, but with the realization that they are *parasitic diseases* which devastate the

human race in the Tropics, we can hope to make these richest countries of the globe accessible to our culture.

Though there is general agreement about the importance of the hookworm fight in heavily infected countries, the method of procedure in the Tropics is still in question. That method is quite different according to whether, on the one hand, we try to stamp out the disease entirely (as we did practically in the North European coal mines), or whether, on the other, we try only to reduce the number of hookworms in the individual so far that the population is clinically no longer suffering, and this, in spite of the fact that the percentage of hookworm-carriers in the population may not be materially reduced. Ashford, Schüffner and Baermann in Dutch India, and lately also Darling and Smillie of the International Health Board of the Rockefeller Foundation — which has devoted so much of its humanitarian work to the hookworm fight — have adopted the latter point of view in the fight against hookworm in tropical countries.

That it is possible to make a population healthy (so far as freedom from hookworm is concerned) simply by treating the patients with anthelmintics, is shown by Ashford. I can only say that I am perfectly in agreement with all of his opinions. Surely, if it is possible to educate the population, not only to build, but also properly to use latrines, as Dr. Washburn was able to do in Jamaica, the latrines will greatly help to reduce the soil infection. On the other hand, as Baermann, Darling, and others have pointed out, insufficient and dirty latrines are more dangerous than useful. In the Dutch-Indian plantations controlled by Dr. Baermann, in spite of the excellent sanitation, the number of hookworm-carriers is still about 98%, as it was about 15 years ago before the sanitation methods had been instituted. This fact indicates how difficult it is to reduce the "hookworm-index" in the tropics in spite of good sanitation. On the other hand formerly, the annual death rate of the coolies was 4%, but today, after periodical treatment of all the population of the plantations, twice a year, with anthelmintics, the coolie death rate is only about 0.5%; moreover, the number of normal births is ten times what it was!

Dr. Washburn (*Closing the Discussion of His Paper*). — The discussion of Colonel Ashford was very interesting, especially in regard to the relation between an improvement in the physical condition and a rise in the percentage of hemoglobin. Here in Jamaica, we have confined our hemoglobin tests to school children. By the use of a modified system of Binet tests we have shown that, following treatment, the mental improvement has been considerable, and that it increases with the increase in the percentage of hemoglobin.

The percentage of hookworm infection in Jamaica — taking into account the entire population of demonstration areas — is about 80% in the rainy, mountainous districts, while in the dry plains, it is only from 15 to 25%.

In Jamaica, the local boards of health (*i.e.*, the parochial boards elected by the people) are responsible for rural sanitation. The plan employed in St. Mary Parish, where we work at present, is to have every householder build his own latrine. When a family builds a latrine for itself, the members of the family are especially interested in seeing that it is maintained; whereas if the latrine is built by Government, the family is much slower to become interested in its maintenance.

Another factor in the almost perfect coöperation we have received from the population of Jamaica, is that the people of the better classes have set an example of helpfulness that is followed by the laborers. This is especially true of the medical profession, the ministers, the estate-owners and managers, and the teachers. We have enjoyed the full confidence and coöperation of all these.

As to the personal benefits (aside from health) derived from treatment, I must tell you a humorous incident about a patient I knew in Trinidad. As this man, an East Indian, was being carried past our office on the way to the district poor-house one of our clerks observed that the fellow had all the signs of heavy hookworm infection. Upon our taking the matter up, a friendly coolie, living near the office, offered to keep the patient — Seemungal by name — while he was being treated. At the time of first treatment, Seemungal wore no clothing except the usual breech cloth. A week later, when he came for a second treatment, Seemungal wore a hat in addition to his breech cloth. At the time of the third treatment he had trousers, also. And at the fourth treatment, a shirt and a pair of shoes had been added. Upon being cured, to especially celebrate his complete restoration to health, he changed his name from Seemungal to Mr. Christopher Padmore.

Dr. Lecesne mentioned a very interesting letter written by a patient who, after being cured of hookworm disease, felt so well that he got into a fight and so was threatened with court proceedings. The letter is as follows:

Dear Dr. Washburn:

I write to complan erbout the hookWorm medsin. It is too stronge and has caus me a lot of trouble. From sins I tak the medsin two treatment I feel stronge an well in boddie an min an like work more than before. The which is all very well.

But, Dr. Sir a grate change have come over me in other ways.

From till I tak the medsin two treatment I was mild an of a sweet disposition an were known by sich throughout the country roun erbout. An very patient. Now Sir all is chang and I feel quite civil to myself. So much so that on last Satday when one Jeptha Smith cuss me I box him down too hard and him now threaten to run law wid me.

Sir from your kindness if the aforesaid person run law wid me I respectful ask you to see His Honour for it were no other than the hook Worm medsin make me act in sich a fierce manner.

Expectin your kind help if need be an you indulgence ever crave I

remain, as of ever

Your patient,
(Sgd) Abijah Thomas

As to explanation of methods of examination and treatment, asked for by Dr. Deeks, — we employ a levitation method of examination, and a patient is not pronounced cured until a specimen, submitted after treatment, is found to be negative. Our routine of treatment is as follows:

1. *Drugs Used.* — (*a*) Thymol, (*b*) Oil of Chenopodium, (*c*) Compound Jalap Powder, (*d*) Magnesium Sulphate.

For an adult, Thymol is given in doses of 40 grains; Oil of Chenopodium in doses of 24 minims; Compound Jalap Powder in doses of 30 grains; and Magnesium Sulphate in doses of from ¼ to 1 ounce.

The Compound Jalap Powder is employed as a preliminary purge; and, also, it is mixed in capsules with the Thymol and the Oil of Chenopodium, for treatment. Magnesium Sulphate is given to any patient whose bowels do not move freely after the treatment is given.

The treatments are administered in the following order: a first treatment of Chenopodium; a second treatment of Thymol; a third treatment of Chenopodium; and a fourth treatment of Thymol. After the fourth treatment, Thymol is employed exclusively.

Treatments are given at intervals of at least one week. Microscopic re-examinations are made after the second and the fourth, and after each subsequent treatment, until the patient is cured.

2. *Preparation of the Drugs.* — The drugs, with the exception of the Magnesium Sulphate, are dispensed in capsules that are prepared at the office. Treatment for adults is placed in capsules of the "000" size.

One capsule will hold approximately 20 grains of *Compound Jalap Powder.* Two such capsules constitute a preliminary purge.

For this preliminary purge, a small amount of powdered charcoal is mixed with the Compound Jalap Powder to give the capsules a dark color that distinguishes them from the treatment capsules of Thymol and Compound Jalap Powder.

In the preparation of *Oil of Chenopodium*, 10 grains of Compound Jalap Powder are placed in a capsule, and 12 minims of Chenopodium are dropped upon this powder. Two such capsules are one day's treatment. (It should be noted that an ordinary pipette will not drop one minim of oil of Chenopodium at a drop, so it is necessary to find how many drops from any given pipette it will take to make 12 minims.)

Thymol is finely powdered, and mixed with equal parts of Compound Jalap Powder; one pound of powdered Thymol contains, approximately, the same volume as one pound of Compound Jalap Powder. This mixture is placed in the capsules, each capsule holding approximately 10 grains of Thymol and 10 grains of Compound Jalap Powder. Four such capsules are one day's treatment.

3. *Details of Treatment.* — On the afternoon before the treatment for the hookworm infection is given, a preliminary purge of 40 grains (2 capsules) of Compound Jalap Powder is administered, between 3 P.M. and 4 P.M.

On the day of treatment, at 6 A.M., if the patient's bowels have moved, one-half of the prescribed dose is administered (1 capsule of 12 minims of Chenopodium, if a First or Third Treatment, or 2 capsules of 10 grains each of Thymol, if a Second or Fourth Treatment). At 8 A.M., the other half of the dose is given. At from 10 A.M. to 11 A.M., if the patient's bowels have not moved freely since the treatment was given, a small dose of Magnesium Sulphate is administered.

The above-described routine method of treatment is given to all strong, adult patients, except those suffering from acute diseases (such as malaria, rheumatism, and dysentery) and those who have indications of kidney trouble.

SPLENECTOMY: WITH REPORT OF A CASE

B. M. Phelps, M.D.

It might appear that indications for splenectomy would occur frequently in the Tropics. A large percentage of all patients entering the hospital in our district have the spleen enlarged to a greater or less degree. Splenomegaly, other than malarial, is seen very rarely in our service. Though the literature on the functions of the spleen and the end results of splenectomy in a variety of diseases is voluminous, there seems to be a marked difference of opinion on the subject among the various writers. Krumbhaar[1], in his splendid article, has collected a total of 1,073 splenectomies done for medical diseases of the spleen, with a post-operative mortality of 17.6 per cent and an apparent cure in 177 cases. The 3 most common conditions for which the operation was done, were pernicious anemia, splenic anemia, and malarial splenomegaly.

This author is of the opinion that splenectomy for pernicious anemia is being neglected. He is of the opinion that splenectomy should be done in those cases brought to our attention early in the course of the disease with a fair blood-picture, fair general condition, an enlarged spleen, and increased hemolysis, and he quotes cases that have shown marked temporary improvement. Similar mention is made of hemolytic jaundice, Banti's disease, and leukemia, with the operation recommended in selected cases. Splenectomy in cases with chronic sepsis is discouraged, on account of the high operative mortality.

> In luetic and malarial splenomegaly not only are the patients' conditions directly improved by removal of the spleen, but they are also usually rendered much more amenable to specific treatment, to which they may previously have proved intractable. In fact, if I may venture an opinion on what is more directly a surgical problem in such secondary splenomegalies, the question

[1] Krumbhaar, E. B., "The Hemolytopoietic System in the Primary Anemias with Further Note on the Value of Splenectomy." — *Amer. Journ. of the Med. Sciences*, Sept., 1923, No. 3, Vol. clxvi, p. 329.

being mainly one of operative risk, it would seem desirable to limit the operation to chronic cases that have proved resistant to all other forms of treatment, and to proceed with extra conservatism where many adhesions multiply the chances of shock and hemorrhage.

Morowitz[1] believes that splenectomy should be a last resort after all therapeutic remedies have failed, provided the spleen is enlarged. Epinger, however, attaches no importance to the enlargement of the spleen as an indication for operation, and does not recommend splenectomy for leukemia and erythremia, reserving roentgen irritation for the latter.

We find that Carslaw[2] and his associates are very conservative in attacking the spleen for leukemia and Hodgkins' disease; and usually the only cases of pernicious anemia recommended for operation are those in which the patient's health is chronically poor; if repeated attacks of splenic pain occur; if, from its size, the spleen is distressing; and, above all, if the danger of hemorrhage seems to have intervened. The mere finding of splenomegaly, especially so in malaria and syphilis, is no excuse for operation.

In Horgan's[3] very interesting case, the patient had suffered for 17 years and was becoming progressively worse. At the age of 20 he had had a gastro-intestinal hemorrhage, and another 5 years later. Gastric ulcer was diagnosed and gastro-enterostomy done. Later the abdomen was repeatedly tapped, on account of ascites, and a total of 127 gallons removed. Examination showed an hypertrophied spleen almost filling the left side of the abdomen. The red-blood cells were 2,500,000, white-blood cells 7,700, and hemoglobin was 51%. A diagnosis of splenic anemia was made, and the markedly enlarged spleen was removed. The patient gained 50 pounds in weight, and the condition of the blood showed steady improvement. In a case of this type there can be no question as to the advisability of operation, and if it had been

[1] MOROWITZ, P., "Extirpation of the Spleen." *Klinische Wochenschrift*, Berlin, p. 769, April 15, 1922, 1, No. 16.

[2] CARSLAW, J., KETTLE, E. H., and DALZIEL, K., "Surgical Treatment of Non-traumatic Affections of the Spleen." *British Med. Journ.*, London, Dec. 23, 1922, 2.

[3] HORGAN, E. J., "Splenectomy in the Treatment of Splenic Anemia." *Virginia Medical Monthly*, Richmond, Feb., 1923, 49, No. 11, p. 652.

undertaken earlier it would have prevented much unnecessary suffering, though the disease must have been of an unusually benign and chronic type to run over such a long course of time without fatal results.

Brill and Rosenthal[1], and Hitzrot[2] report splenectomy for hemorrhagic purpura with brilliant results, and more recently Cohn and Lemann[3] have reviewed the literature on this particular aspect of the spleen in relation to disease, and have reported a case which has shown constant improvement up to 6 months after operation.

In malarial splenomegaly the predominant question is: To what degree of disability are we to allow the patient to develop before resorting to removal of the spleen in an attempt to give relief? The spleen which is enormously enlarged, or which by its weight and a relaxation of the pedicle has become dislocated, may totally incapacitate the patient for his usual duties. There is also the liability of some slight injury causing a rupture, though at necropsy we have found most of the very large spleens to be fibrotic and far from friable. Few of the class doing manual labor can afford the time lost during the protracted treatment with internal remedies.

If we can operate on these patients while they are in a fair condition, limiting their stay in the hospital to about 2 weeks, and send them back to their work entirely well and with the same opportunity of living out their allotted span as before operation, this must be the ideal method of treatment. But, however dogmatic the assertion may be, we do not believe that the patient who has been splenectomized has the same possibility of long life and resistance to concurrent diseases as the one who has been left with his large or dislocated spleen, irrespective of the degree of damage that it has sustained. We mention, now, a case which, to a certain degree, illustrates the fact that in doing a patient some

[1] Brill, N. E., and Rosenthal, N., "Curative Treatment, by Splenectomy, of Chronic Thrombocytopenic Purpura Hemorrhagica." *American Journal Medical Sciences*, 166, 469–624, Oct., 1923, p. 503.

[2] Hitzrot, J. M., "Splenectomy for Haemorrhagic Purpura." *Annals of Surgery*, 78: 129–304, p. 185.

[3] Cohn, Isidore, and Lemann, I. I., "Splenectomy as a Treatment for Purpura Haemorrhagica (Thrombo-Cytolitic Purpura, Kaznelson.)" *Surgery, Gynecology and Obstetrics*, May, 1924, Vol. xxxviii, No. 5, p. 596.

good we may apparently open the way for a great deal of harm.

REPORT OF A CASE

Mrs. S—S, intelligent Chinese woman, aged 35 years, has had 8 children, the youngest being about 3½ years of age; entered the hospital on May 8, 1922, complaining of constant dragging pain in the right lower abdomen, — had noticed a large lump in the abdomen for more than 3 years. This she considered as the "womb" and had been told by a surgeon that she had a "fallen womb," and operation for this condition had been recommended; has had "fever" many times including the past 4 days; menstruation normal, in time and amount. *Physical examination* shows a slightly emaciated and anemic Chinese woman; there is a visible protuberance in the right lower quadrant of the abdomen. On palpation, the mass is smooth, slightly movable, having connection with the right pelvic cavity, from which it cannot be lifted, and has a distinct sharpened and notched border. Uterus is in good position and adnexa negative. No spleen could be palpated nor percussed in the normal splenic area. Examination otherwise negative. The blood was negative for plasmodia, urine negative, stools showed Ankylostoma ova. Splenectomy was advised and refused, the temperature remained normal, and the patient left the hospital on the 5th day after admission.

This patient returned to the hospital on December 7, 1922, complaining of the same symptoms in the pelvis, as well as "fever" for the past month. The physical examination was the same as on the previous admission. Tertian parasites were found in the blood in moderate numbers, hemoglobin was 60%, white-blood cells 7,000, red-blood cells 3,200,000, polymorphonuclears 48%, large lymphocytes 8%, small lymphocytes 44%, Wassermann negative. Urine showed a few hyalin casts, and in the stool eggs of Trichocephalus Dispar. The patient was given intensive quinine treatment for 5 days, during which time the temperature remained normal. On the 6th day after admission, ether was administered and the abdomen was explored thru right rectus incision. The uterus and adnexa were normal, gall-bladder and appendix normal; a very large spleen was

wedged into the pelvis in such a manner that some difficulty was experienced in removing it. The large vascular pedicle was doubly ligated, covered over with peritoneum, and the abdomen closed in the usual manner. Though the spleen was bled for transfusion, this did not prove necessary and the patient left the operating room in excellent condition. The spleen (after bleeding) weighed 4 pounds, 5½ ounces (1.75 kilos).

For 5 days following the operation the temperature fluctuated between 99 and 102 degrees Fahrenheit, after which it returned to normal, and the patient was discharged on the 12th day after operation. There was no wound infection. On the 5th day after operation, the leucocytes numbered 16,000 and on the 11th day 12,000. Unfortunately the condition of the red-blood cells is not mentioned in the laboratory report.

On November 1, 1923, this patient returned to the hospital, on account of "eruptions" of the skin of the face, neck, hands, forearms and arms. There had been no return of the disability caused by dragging pain in the abdomen, she had gained nearly 40 pounds in weight, and was nearly 5 months pregnant. Appetite has been good, and the diet a general one. Examination showed a general dehydration and redness of the skin of face, neck, arms and forearms; and the dorsum of hands was cracked with serous weeping. The lesion seemed more predominant on the most exposed surfaces. Laboratory reported tertian parasites in the blood, few hyalin and granular casts, and a stool infection of *Ascaris lumbricoides*.

Blood-picture. — Hemoglobin 75% (Talquist), total leucocytes 9,500, polymorphonuclears 75%, small lymphocytes 9%, large lymphocytes 15%, eosinophiles 1% — *aniscytosis poikilocytosis* and *poly-chromatophilia* very marked — few stippled erythrocytes with 1 to 2 normoblasts in every field.

The skin lesion proved very stubborn, but patient was discharged well of the disease on November 26, 1923. We were advised that this patient died in an adjacent town, early in January, 1924, after a very brief illness. We were unable to obtain further details, as it appears that there was no physician in attendance. The husband of the patient states that there was a return of the skin condition a few weeks after her leaving the hospital.

SUMMARY

1. Attention is drawn to the multitude of optimistic reports of writers who have removed the spleen for the cure of various medical conditions in which the spleen is deemed to be the focus of the pathological condition.

2. A case of splenectomy for a dislocated malarial spleen causing pain and disability, is reported. The direct result of this operation appeared to be excellent, but the patient survived less than 2 years, and there was a severe blood dyscrasia at the time of death.

3. The possibility of a subtotal resection of the spleen, as in operations on the thyroid, is suggested.

DISCUSSION

Dr. A. A. Facio (*Opening the Discussion*). — In the first place, I wish to congratulate Dr. Phelps on his very interesting address. I fully agree with him in the conclusion of his remarks. My experience with cases of spleen-enlargement has led me to believe that there are, rigorously, only 3 conditions in which the spleen should be removed; first, malignancy; second, traumatism; and third, when the spleen is dislocated or has become so large that it produces severe pressure-symptoms not mentioning, of course, certain cases of leukemia where removal of the spleen certainly greatly benefits the condition of the patient, though also only temporarily.

The mortality which follows splenectomy is so high, even in the hands of very skilled surgeons, and the results show so little encouragement in the majority of cases, that, unless one of these 3 conditions has presented itself, it does not seem to me to be worth while to perform splenectomy. Although marked improvement follows the successful operation, the life of the patient is usually shortened; as a general rule, the patient lives only from 1 to 5 years after splenectomy has been performed.

This is what I have gathered from my own experience, and from some of the statistics which I have consulted. I sincerely believe that splenectomy performed for the relief of malaria or syphilitic cases should never be done, because the improvement which follows is never permanent, and, as a matter of fact, I think more harm than good is done when splenectomy is performed.

Dr. Foster M. Johns. — In view of the reference made to the case presented by Drs. Lemann and Cohn, I wish to state that I have very recently studied the blood-picture and find the platelet count low, but otherwise perfectly normal. Splenectomy was resorted to here only in the face of the gravest emergency, the pa-

tient being almost exsanguinated, and there is no doubt in my own mind that in this instance the operation was a direct life-saving one.

A case of Dr. Urban Maes, of New Orleans, has not been reported as yet and, as I believe it is worth recording here, I will take the liberty of reporting it: —

This lady had progressed with a diagnosis of pernicious anemia to the extent that death was apparently only a few weeks off. As there was some evidence that the anemia may have been initiated as a hemolytic jaundice, splenectomy was performed, with the result that improvement began rapidly and has been continuous for now nearly 3 years. At present there is no anemia — with a moderate polychromatophilia only. One of the transfusions resulted in the transmission of syphilis, but I do not believe the specific treatment the patient has received vitiated the importance of splenectomy in her recovery.

I believe very strongly, with Dr. Phelps, that splenectomy is in the experimental stage, and should not be performed for *medical* purposes, at least except in very urgent cases where a complete diagnosis can be obtained.

Dr. Edward I. Salisbury. — I should think that the English, perhaps, would have some statistics on the removal of spleen in traumatic conditions. It was a standing joke in England that the old Colonials, years ago, returned from India with such large spleens that if one sat down very hard he was in danger of rupturing it. I am sure there was a basis of fact in the joke, and that there were cases from which statistics can be drawn as regards the duration of life after operation for traumatic rupture.

In Panama we have very few cases that warrant operation for a medical condition, nor do we favor surgical intervention. A few operations have been performed at the Ancon Hospital. I had one experience of my own, in 1916, when one night I assisted Dr. Runyan in removing the spleen of a dredge operator, a strong, robust man, who had been drinking for several days before. He was taken to jail, where he stayed for 3 days, supposedly drunk, but it was finally realized that he was sick. He was brought to the hospital with all the symptoms of hemorrhage, — the abdomen was soft and doughy.

We operated, and found a large quantity of free blood in the abdomen, and a spleen enlarged to many times its normal size. It was 8 or 9 inches through, with cracks all through the capsule from subcapsular hemorrhage. A little over a year after the removal of his spleen, this man returned one night with acute intestinal obstruction. We again operated, and found that the obstruction was due to a large tangled mass of mango-fruit fibre.

The blood picture did not show anything outside what we ordinarily get in current "tropical anemia." I have not heard from this patient since that time.

Dr. B. M. Phelps (Closing the Discussion of his own Paper). — This paper was intended primarily to draw attention to the fact that removal of spleen for cure of malaria or syphilis, is an extremely dangerous method of treatment. However, as to the good results, I think that Krumbhaar, in his very comprehensive monograph, which is the latest thing published, so far as I know, shows that in 1,077 splenectomies done for a variety of causes — medical diseases of the spleen — there were 117 cases of probable cure, which is a very small number indeed. We admit, of course, that in all cases such as malignancy or rupture of the spleen, there is no question whatever — we must remove the spleen.

NOTE ON RETINO-CHOROIDITIS WITH RELATION TO AN UNBALANCED DIET IN THE TROPICS

D. F. Reeder, M. D.

(*Read by W. M. James, M. D.*)

Retino-choroiditis is a serious affection. This note deals with that form of *Retino-choroiditis* associated with *Uveitis* and resulting in a cloudy vitrous, with impaired vision; it may be in one or in both eyes. The impairment of vision noted may be only spots before the eye, or it may terminate in complete blindness.

In the treatment of this condition it is necessary to determine, if possible, the exact etiology. In the class of cases to be dealt with in this note, those are not included which are caused by syphilis, diabetes or Bright's disease, nor that class of cases caused by focal infection, such as sinus disease, abscessed teeth, and infected tonsils.

There is a large percentage of cases in the Tropics of *Retino-choroiditis*, the etiology of which is none of the above. A certain percentage of these cases, in our experience, is due to faulty diet, principally a diet consisting, for the most part, of carbohydrates.

It has been noted that cataracts develop more frequently in people with diabetes than any other class of cases, so much so that future investigations may show that the chemical action of the sugar is in some way responsible for the forming of cataracts. So it is no more than reasonable to assume that it would more readily affect the choroid which has a much greater blood supply.

The successful treatment of these cases is not a problem only for the oculist — it is necessary to have in consultation an expert medical man. A low carbohydrate diet, as outlined by Dr. Deeks, has given excellent results in the treatment of these obstinate cases when all other methods have failed.

DISCUSSION

Col. Bailey K. Ashford (Opening the Discussion). — I wish to testify to the fact that I think I have seen cases of *Retino-choroiditis* due to faulty diet — excessive carbohydrates. I have in mind the case of a wealthy woman in whom all other causes were excluded. I sent her to an oculist, — he diagnosed her condition *Retino-choroiditis*, and I had very little doubt, nor had he, that it was due to excessive carbohydrates.

Dr. Roland C. Connor. — Just a few words regarding the cases of *Retino-choroiditis* in the medical clinic of Ancon Hospital, as we very often have cases, referred to the Medical Clinic from the Eye Clinic, in whom none of the common causes that Dr. Reeder has spoken of in his note can be connected with this condition. I have advised routinely a change in diet, reduction of carbohydrates, and increased quantity of green vegetables, and without any exception I don't remember that I can recall a case that has not improved or had the disease arrested, when the diet was followed.

We have had cases in negroes where there was no possibility whatever of getting coöperation in this respect, but with the whites this procedure has worked wonderfully well and has been uniformly successful. One recent case in question was that of an official of the Panama Canal who practically lost the vision of one eye before he would adopt his proper diet and get relief. Finally he did, and though he nearly lost the vision of one eye, he saved that of the other.

Dr. W. M. James (Closing the Discussion). — I should like, in closing this discussion, to fulfill a promise made to Dr. Reeder, who asked me to put him on record that it is due to Dr. Deeks that in these cases we have used a very low carbohydrate diet in treating this serious condition.

I do not know how much personal experience other members of this Conference may have had with this type of *Retino-choroiditis* but in our clinic we see from 25 to 50 cases every year. In some there is complete blindness in one eye, due to optic atrophy; and in others, marked loss of vision in one or both eyes. This is a most unfortunate condition, and one which, if not checked, results not only in physical inconvenience due to the blindness, but in great mental anguish as well. Therefore, I think it is not amiss to take a few minutes in impressing upon you the importance of treating this condition, which generally comes within the province of the oculist, but which can be suspected by any medical man to whom the patient comes with a history of spots and threads before the eyes.

One of the most notable examples of this kind was the case of a gentleman who was very prominently connected with the construction and building of the Panama Canal. He had been told by most eminent oculists in the United States that the loss of his vision was only a matter of a few months, and he was naturally very greatly depressed. He denied that he used an excess of carbohydrates in his diet, but a careful check resulted in the finding that he lived almost entirely on carbohydrates, although he was not aware of it himself. A change in his diet resulted in a great improvement in his sight, though we did not obtain a complete cure.

Another case was that of a lady, whom we saw recently, who had for some years lost complete sight in one eye, and was fast losing it in the other. She was large and over weight. She had high blood-pressure, no casts nor albumin in the urine, and her blood chemistry was normal. She also denied the use of an excess of carbohydrates, but upon consulting other members of her family we found that she did use an excess quantity. It is not that patients wish to create a false impression in regard to the excessive use of carbohydrates, but they are entirely unaware of the unbalanced proportion of their diet. In a month the sight in this woman's remaining eye was entirely restored to normal, and has remained so.

These cases may seem to be of slight importance, but I assure you the patients take a different view, and are very grateful for the improvement.

TRACHOMA AND PANNUS

Miguel Arango, M.D.

It is on account of trachoma being so widespread among the people of some tropical regions, giving rise to confusion with certain states of conjunctival folliculosis, that we have thought it of some importance to bring to this learned meeting these short comments on that disease. Besides, during our practice, we have been able to observe some frequent complications, such as pannus, which are somewhat different from those observed in other localities.

Although the true etiological factor of trachoma is still unknown, it may be accepted that it is due to an infective agent; the fact thereby being explained that it is contagious and that the lack of personal hygiene, as well as other means of infection, assists in its propagation.

We may say that trachoma is an inflammatory infiltration of the adenoid tissue of the conjunctiva, where there occur a development of follicles and an increase of the papillary structures placed beneath the mucous membrane. It is, according to Fuchs, the hypertrophy of the conjunctiva that forms the most characteristic feature of the trachoma. It is from the roughness of the conjunctiva, caused by that hypertrophy, that the disease has in fact received its name.

Now, since the adenoid tissue of the conjunctiva is the one mainly affected in trachoma, any other morbid cause which affects the same tissue may produce conditions of the conjunctiva with the appearance of trachoma. It is easily understood that if trachoma is produced by an infectious agent acting mainly on the adenoid tissue, any other cause that affects the same structure may act as a predisposing cause to the above disease, making easier the development of its agent.

And it is possible to admit that in practice the various forms of trachoma are probably stages or variations of the same disease; and that there are many degrees in follicular conjunctivitis which, together with trachoma forms, make a complete and gradual series of morbid states.

The conjunctiva from the ciliar edge to the fornix is of adenoid character; that is to say, it contains a great many lymphatic corpuscles, which increase in number with the slightest inflammation, resulting in the formation of follicles by its accumulation. This is prone to happen in lymphatic pretuberculous subjects. In a normal conjunctiva the papillary characters, found in all the mucous membranes of dermic source, are very slightly marked, but in some lymphatic children enjoying good general health one may see in the fornix many small elevations of follicles raising up the conjunctiva. This may persist for a time without invading the physiological boundary line, and this state may be called *physiological folliculosis.*

Now if the anaemia and lymphatism are augmented, as in pretuberculous children, those normal follicles which are the seat of proliferation get larger in size; and all this, without producing local troubles. There are no signs of inflammation of the mucous membrane, and, to tell the truth, this development of follicles without conjunctivitis may be taken as a transition from the physiological to the morbid state. It is what de Schweinitz proposes to call *folliculosis of the conjunctiva.*

To the above condition of the mucous membrane may be added any occasional form of infectious agent which leads to a true inflammatory process more or less intense. All these superimposed factors may assist in causing the condition to develop from mere hyperaemia of the conjunctiva to real inflammation of this membrane. So in this way an inflammation is added to the somewhat physiologic folliculosis, and hence results the condition called *follicular conjunctivitis.* Among the above-named superimposed causes we may mention the continuous use of medicinal drops, certain errors of refraction, and infections like influenza and measles (which we have lately seen produce, at times, an intense conjunctivitis and show streptococci and staphylococci); and, as a matter of fact, the degree of the follicular conjunctivitis varies directly with that of the superimposed conjunctivitis.

Let us see what de Schweinitz says regarding the different degrees of folliculosis: — "Follicular conjunctivitis may be admitted if the small red elevations are associated with signs of inflammation; folliculosis of the conjunctiva, if those signs are absent."

Follicular conjunctivitis may be taken as a kind of catarrhal conjunctivitis, and many of the causes of the latter act as exciting causes of the former.

This follicular conjunctivitis has been called *school folliculosis*, on account of its being the form more frequently observed among school children.

We have met with this affection in public schools, and in a great number of children there is also hypertrophy of the tonsils (as many as 60% of the cases), but, on the other hand, the rate of error of refraction is very low.

It may be acknowledged that some cases of follicular conjunctivitis are contagious, on account of absolute carelessness, by means of the secretion which carries infectious agents, as is the case in catarrhal or exanthematous conjunctivitis; and the communicability is easier if there are lymphatic conditions.

At times this follicular conjunctivitis is neglected and persists for a long time, and then the adenoid tissue develops, the follicles already formed get larger and larger, and even with a slight degree of oedema of the conjunctiva it is difficult to distinguish this condition from the trachoma granules.

Dr. May advises, in cases like this, to wait until after several weeks of treatment before making a definite and final diagnosis; for in some cases of folliculosis, follicles disappear, leaving the conjunctiva normal, while in trachoma they persist and there are permanent changes of the mucous membrane.

Let us see how de Schweinitz considers some cases:

> Much difference of opinion exists as to whether folliculosis should be placed in a separate category from granular conjunctivitis, or whether it should be regarded as an early stage of the latter disease. Although transitional forms apparently exist, the evidence, clinically at least, warrants the belief that this affection is distinct from granular lids, because folliculosis occurs where trachoma is unknown, and because the follicles disappear without leaving a trace of their existence or producing scar-tissue in the conjunctiva.

Finally Dr. May says that follicular conjunctivitis is "an obstinate form of the catarrhal conjunctivitis," and he believes that the former is one of the first stages of trachoma.

The most intense cases of follicular conjunctivitis we have seen have been in lymphatic young children, in whom the tonsils were enlarged after the children had suffered from influenza, measles, or whooping cough. In 75% of these children the ocular affection was so intense as to show in some of them the trachomatous aspect.

From the foregoing, we may conclude that in chronic, advanced follicular conjunctivitis the adenoid tissue may be invaded by a special agent and produce trachoma, both the formation of trachoma follicles and the thickening of the mucous tissue itself taking place, which might afterwards be the cause of a sclerosing process.

In short, the conclusion we wish to draw is that in trachoma, although it may develop without folliculosis or follicular conjunctivitis existing previously, this latter condition is frequently a predisposing cause which helps a great deal the development of trachoma.

It has been seen that the follicles of the conjunctiva may be produced by many causes, and we ought to bear in mind, in the matter of diagnosis of follicular conjunctivitis, Fuchs' assertion that the hypertrophy of the conjunctiva, together with the development of follicles, is very characteristic of trachoma.

In folliculosis of the conjunctiva, and even in follicular conjunctivitis, there is no sign of thickening of the lids, though there may be a fullness in the advanced cases. On everting the lids we can see the lymphoid follicles more or less extended over the lids, and in advanced cases the follicles arrange themselves in crescentric rows from one canthus to the other, separated by furrows, but the follicles still have a smooth transparent appearance. These follicles are so superficially situated under the epithelial layer of the conjunctiva, that they do not appear as an integral part of the conjunctival tissue. As the conjunctiva does not show any hypertrophy, it retains its elasticity. There is no tendency for the surface to bleed. The color of the follicles is pink, and if there is not much inflammation, the majority of cases show no change in the color of the conjunctiva. The minute blood vessels may be followed from the ciliary border to the fornix without interruption. If there is any secretion, it is thick, mucopurulent and sticky.

On the other hand, in trachoma the conjunctiva is red and considerably thickened; its surface shows the characteristic trachoma granules, which appear as an integral part of the conjunctival structure itself, with a certain amount of hypertrophy. On account of this hypertrophy, the blood vessels are not well seen, and it is not possible to follow them as in folliculosis. Surgeon John McMullen insists on the appearance of the blood vessels, as indicating the degree of the conjunctival hypertrophy, a very essential feature of trachoma. The secretion, if any, is thin, watery and acrid in non-complicated cases at least.

Finally, while in trachoma the hypertrophy gradually disappears and is replaced by cicatricial tissue, in the folliculitis there never is any cicatricial process, and the conjunctiva may return to its normal state.

From the foregoing we may say that the main elements of clinical diagnosis in uncomplicated cases of folliculosis are the retention of normal elasticity of the conjunctiva, the absence of hypertrophy of the membrane itself, the non-existence of trachoma granules, the fact that the blood vessels may be traced, and the character of the secretion as already mentioned.

"With the bacteriological side of the diagnosis of trachoma," said Dr. Garhart in an important paper, "we, as clinical physicians, have little to do; and this is perhaps fortunate because the particular microörganism causing trachoma has not yet been definitely isolated."

As regards the several forms of trachoma, it may be briefly said that acute trachoma is rare, and then it is sporadic and begins with symptoms of an acute catarrh, with the formation of follicles. The great majority of these cases are mixed states; that is to say, an acute infection, such as that of the Weeks' bacillus, or pneumococcus, or even the gonococcus more or less attenuated, is superimposed upon the trachoma infection where the course is chronic in itself. It is natural that these acute states may also be caused by physico-chemical agents as medicamental measures.

In the acute stage of the trachoma infection, there is a watery or mucopurulent secretion and it is in these cases that the disease becomes more contagious; for in its usual

chronic and dry form the disease is only mildly contagious. What is called acute trachoma is markedly contagious, and those are cases that must be excluded entirely from school or, as they are in the United States, segregated in special ophthalmic classes.

The secretion, assures Akenfeld, not only shows the above-mentioned bacilli as agents of the added infections, but there are many cases that prove that the secretion is specifically contagious as regards trachoma.

In many instances operators for trachoma, as well as nurses assisting in the operating rooms, were taken down with an acute inflammation of the eye which afterwards developed into characteristic trachoma. Most probably the infection came from small particles of trachoma tissue which went into their eyes when the trachoma follicles were expressed. Dr. H. Woolong observed cases of direct infection with trachoma which began with all the symptoms of an acute conjunctivitis that are seen in Koch-Weeks infection; but a few weeks after, abundant trachoma follicles were observed in the fornices of both lids.

As a rule trachoma is insidious and chronic in its course, and when it appears in an acute state there is an added cause, and the secretion of a mucopurulent character is infectious, both for the superimposed infection and for the trachoma, and both of them may be transmitted at the same time. We may add that as the transmission of trachoma is more frequently observed during that acute stage, it may happen that in the great majority of cases the trachomatous agent is easily grafted into the conjunctiva after the added conjunctivitis is produced, or even in other circumstances, by the slight degree of hyperemia produced in eye-strain.

It is quite clear from the foregoing statements that we may draw two important conclusions: The first is, that the usual chronic and non-secreting form of trachoma is slightly contagious; and the second, that normal and healthy eyes, which are free from all source of irritation, may resist the direct trachoma contagion.

The above consideration explains well why trachoma, although very contagious, is not extended over a large area. It is quite true that occasionally there appear many cases

of trachoma after influenza, measles and whooping cough epidemics, and as a result of the conjunctival irritation following these diseases.

As far as the other forms of trachoma are concerned, they are simply variations of the same disease, which may all end in the stage of cicatrization. So, according to the clinical manifestation of the disease, various types — papillary, follicular or granular, mixed gelatinous, sclerosing and cicatricial trachoma — have been described.

There is one form, designated by Knapp as non-inflammatory follicular trachoma, in which the granulations develop in the conjunctiva without evidence of inflammation, and which have been regarded as analogous to nasopharyngeal adenoid hypertrophy.

If we have insisted on the importance of this diagnosis, it is because in many cases we have seen great inconvenience caused by such errors.

We quite understand the alarm caused by the existence of trachoma in the United States, the classical land of modern hygiene, as the 5% infection observed in the schools of Kentucky must be a source of great uneasiness. All this explains the strenuous efforts made by the United States sanitary authorities to control the disease, and hence the great display of care by their doctors in this matter. In this connection, we remember that the doctor of one of the boats sailing from Puerto Colombia declined to accept a certain passenger for passage on account of trachoma, although the doctor of the port assured him that it was a case of simple follicular conjunctivitis. To this the doctor of the boat replied: "All that may be so, but I prefer to make a mistake and retain my position than to do otherwise and lose it." By this he meant that in the United States it is more pardonable to mistake follicular conjunctivitis for trachoma than the reverse.

Now, if to this display of care we add the difficulty of the diagnosis in some cases, we can explain the unfairness occurring occasionally. In one instance a personage, with his family, coming from the interior of Colombia, intending to take passage on a boat to New York, presented the certificate of a Barranquilla doctor certifying that they had a certain degree of follicular conjunctivitis. The doctor of the

boat made a diagnosis of trachoma, and therefore did not accept them. The case was taken before the Captain, and by the mediation of third parties the passengers were accepted. In New York they were again examined and allowed to land, as the diagnosis of trachoma was dismissed.

We know of some cases of folliculosis of the conjunctiva, or simple irritation as in eye-strain, which were rejected at Puerto Colombia by the doctor of the boat, owing to a diagnosis of trachoma. Coming back to Barranquilla, they were advised to go to Santa Marta to embark on the same boat; and, using some adrenalin drops before the ocular inspections were made by the same ship's doctor, they were accepted as passengers.

It is, therefore, urgent that sanitary authorities adopt some methods of better organization and that the ships' doctors exercise more care, so as to avoid similar errors and unfairness. And it may be said that, if some care is taken, the diagnosis generally is not difficult, and doubtful cases are very rare.

Pannus Trachomatosus is a frequent complication of trachoma, and, as we have many times observed the form described by Raehlmann, we think fit to say something about it here.

The well-known form of pannus has been called vascular keratitis, and depends upon the formation of new blood-vessels between the corneal epithelia and Bowmann's membrane associated with collection of round cells. In many cases we have observed that, besides the development of blood vessels, there is the formation of lymphoid infiltration, just analogous to the same pathologic condition in the conjunctiva; in short, there is, in cases such as the above, a special implantation of trachoma process in the layers of the cornea.

We have observed this form of adenoid infiltration very frequently in the tropical regions of Colombia, and in the great majority of the cases the vascular keratitis is composed of only a few vessels (*pannus tenuis*). On the other hand, this infiltration takes place not exactly in the upper half of the cornea, which is covered by the upper lid, but in the corresponding part of the horizontal diameter. It takes, in fact, the appearance of the corneal part of pterygium, but is

somewhat interstitial and deeper-seated than the vessels of the ordinary pannus. This kind of adenoid infiltration appears suddenly one day, to go away also in a very short time; and this disappearance happens in spite of the fact that the vessels of the pannus persist.

If we remember that the epithelial and superficial layers of the cornea have the same origin as the conjunctiva, we may better appreciate the development of adenoid cells in the form of pannus. Pannus adenoideus we have mentioned.

CONCLUSIONS

First.—The adenoid structure of the conjunctiva, when affected, gives rise to a complete and gradual series of conditions from the simple folliculosis without local reaction, and follicular conjunctivitis, to the trachoma follicles. We ought to accept at present the dualistic doctrine that there are folliculosis and trachoma; for, although transitional forms apparently exist, the evidence, clinically at least, warrants the belief that folliculosis is distinct from granular lids, because folliculosis occurs where trachoma is unknown, and because the follicles disappear without leaving a trace of their existence or producing scar-tissue in the conjunctiva.

Second.—Follicular conditions of the conjunctiva are more marked in school children (school folliculosis) and especially so after infections like influenza, measles, whooping cough, etc., where the conjunctiva is affected. All this is observed especially in lymphatic and pretuberculous children.

We have found, in 60% of children affected with folliculosis, a tonsil hypertrophy, and on the other hand very few cases of error of refraction.

Third.—In many cases the diagnosis of follicular conjunctivitis is very difficult, and in cases like these we must observe the evolution for some days and examine other members of the family or other possible contacts. But after all, cases difficult to diagnose are very rare.

Fourth.—The main elements of clinical diagnosis in follicular conjunctivitis are, the retention of normal elasticity of the conjunctiva; the lack of hypertrophy of that membrane; the non-existence of trachoma granules; the fact that the blood-vessels may be traced from the ciliary edge to the fornix; and a thick, mucopurulent and sticky secretion.

In trachoma, on the other hand, the elasticity of the conjunctiva is lost; there are hypertrophy of the membrane, which bleeds easily, the presence of trachoma follicles, the fact of the interruption of the blood vessels, and the watery, thin and acrid secretion.

Fifth.—The cases called acute trachoma are trachoma with an infection super-imposed, or at least an irritative state produced by medicinal drops or eye-strain. In all these acute cases there is an infectious secretion which makes trachoma more contagious; for in the usual, chronic and non-secreting form of trachoma the contagion is very limited. It is, in fact, by direct contact with infected persons, and indirectly by contact with articles freshly soiled with the infective discharge of such persons, that the contagion occurs.

Sixth.—We may say that trachoma in its usual form is slightly contagious, and that normal and healthy eyes may resist the infection.

Seventh.—The carelessness in making the diagnosis and the great fear of trachoma have been the causes of doctors' making mistakes which have produced regrettable unfairness.

Eighth.—Pannus trachomatosus appears frequently in the form of vascular keratitis, but we have observed in the tropical regions of Colombia the form described by Raehlmann consisting of an infiltration of adenoid cells in the layers of the cornea. If we remember that the corneal superficial layers have the same dermic origin as the conjunctiva, we are able to account for this adenoid infiltration.

From a practical point of view we may state the following facts:

The source of infection in trachoma is secretions and discharges from the conjunctiva and adnexed mucous membranes of the infected persons. The mode of transmission is by direct contact with infected persons, and indirectly by contact with articles freshly soiled with the infective discharges of such persons. The period of communicability lasts during the time of persistence of lesions of the conjunctiva and of the adnexed mucous membranes or of discharges from such lesions. As regards methods of control, we advise the following measures:

1. Recognition of the disease by clinical symptoms. Bacteriological examination of the secretion will undoubtedly be useful.
2. Isolation, by exclusion of the patient from general school classes. The establishment of special ophthalmic classes.
3. Disinfection of discharges and articles soiled therewith.

As general measures we may adopt:

1. Search for cases, by examination of school children, of immigrants, and among the families and associates of recognized cases.
2. Treatment of cases until cured.
3. Elimination of common towels and toilet articles from public places.
4. Education in the principles of personal cleanliness and in the necessity of avoiding direct or indirect transference of discharges.
5. The foundation of public dispensaries where communicable eye-diseases are treated.

THE PROBLEMS OF MORTALITY AND ACCLIMATIZATION IN THE CENTRAL AMERICAN TROPICS

FREDERICK L. HOFFMAN, L.L.D.

It would seem, at first, as if not much more could be said upon a subject which has been one of interminable discussion and consideration, practically from the very beginning of the white man's settlement in tropical regions. The learned disquisitions on the subject by men of the foremost rank in medicine and sanitation would seem to be conclusive upon many essentials which are generally accepted as finally settled, at least in the minds of the general public. But it requires no extended consideration to convince those qualified to pass upon the evidence that much, if not most, has yet to be learned as regards the conditions under which the attainment of at least normal longevity in the Tropics is not inconsistent with the ordinary vocational pursuits on the part of residents from northern latitudes. The wonderful discoveries, all made during recent years, regarding causative factors responsible for many tropical diseases, have thrown new light upon old questions and opened new avenues of development for the white man's enterprise in the utilization of tropical lands and products. It is now generally conceded that the problem is, in the first place, one of effective sanitation and the implied control of parasitical diseases; and, on the other hand, of correct habits of living, adapted to the so-called tropical climate.

When these two fundamentals are complied with, it goes without saying that, in the large majority of cases, the attainment of normal longevity is not difficult on the part of white residents exposed to tropical conditions of life. What is generally called the tropical climate is frequently misconceived as one of excessive heat, although daily temperature changes in the Tropics may produce a wider range of temperature than, at least, in the sub-tropical sections of the north. That there are regions in the Tropics which may properly be referred to as torrid, goes without saying, but it

seems to admit of no contradiction that, broadly speaking, the temperature is rather that of a warm climate than a hot climate, and that the latter is the rare exception and need, on the whole, give no serious concern. There are regions in the United States, particularly in the Death Valley of California and portions of Arizona and New Mexico, where the temperature during the summer is persistently higher than is met with under normal conditions in any portion of the Central American Tropics and the West Indies. The heat record of the Death Valley and of the Imperial Valley, including Yuma, Arizona, cannot be matched by corresponding conditions in Central America, or the islands of the West Indies. Yet, even in these localities of the southern United States, men attain normal longevity and live industrious lives, primarily because of the absence of conditions otherwise injurious to health, or of habits inconsistent with a normal freedom from disease.

The enormous improvement in the health of our southern states during the last generation bears evidence to the truth of the theory that "the earth, as modified by human action," — can be made habitable and useful for the needs of man when necessity requires, wherever that region may be located, be it in the sub-Tropics, the Tropics, or, for that matter, in the sub-Arctic or the Arctic. It is my deliberate judgment that the main reason for the backward condition of the Tropics is the fact that, in a general way, these fertile regions have not as yet been drawn upon by modern nations as a matter of imperative necessity, and as sources of a needed food supply. When that time comes, the difficulties, which are now largely a matter of academic discussion, will tend to rapidly disappear.

For the present purpose, the term "Central American Tropics" includes all of the islands of the West Indies and the north coast of South America. The geographical situation of this area is fairly contiguous, although the variations in topography and climate are enormous. Conclusions that may be reasonably true for Cuba, or Porto Rico, do not necessarily hold for Jamaica or Trinidad. Likewise, what is true for Guatemala, or Honduras, may not hold for Panama, or the north coast of the United States of Colombia. At the same time, the term "Central American Tropics" is a

convenient one for drawing attention to a region, concerning which, in former years at least, and to a certain extent at the present time, serious apprehensions prevail regarding health and mortality, particularly as affecting temporary or permanent residents, formerly living in the Temperate Zone. It would, of course, be utterly impossible to do full justice to such a question, except in a most general way, and with reference to a few selected localities or sections.

No one has essayed to better advantage upon the general principles of tropical acclimatization than Dr. Aldo Castellani, joint author with Dr. Albert J. Chalmers, of a standard manual of tropical medicine. I would needlessly take up time by discussing matters with less authority than has been done by these two distinguished authors, who have admirably outlined what requires to be considered in matters of tropical climatology, race pathology, and the effects of food and climate on man in the Tropics. In matters of detail much could be said by way of amplification, especially upon questions of race pathology, which is a branch of medical science as yet in its infancy. It is amazing that a wealth of opportunity should have been so long neglected, to study the disease-predisposition of certain races, in the light of modern scientific achievements and by modern means of precise measurement and determination. Regarding our own negro population, there is not yet a science of negro medicine which alone can aid in the solution of the problem as to how the immense disparity in the disease liability of the two races is to be explained. There can be no question of doubt — as regards certain diseases — that the disease resistance of the white man is immeasurably greater than that of the negro; but there are many obscure pathological conditions which require much more extended research before it will be permissible to speak with emphasis upon matters frequently accepted as settled. All of you are familiar with the old theory that the negro was not liable to malaria and yellow fever, although an abundant experience is now entirely to the contrary; but no explanation, for illustration has been forthcoming as to why the negro women of today in our southern states should be so excessively subject to uterine fibroids, which, previous to emancipation, at least, were generally considered as very rare.

There is no acceptable definition of acclimatization, in the medical sense. From the point of view of the general public, acclimatization means a common-sense adaptation to novel conditions of life, and the prevention or control of such conditions as produce consequences injurious to health and life, through measures inconsistent with the performance by a normal man of ordinary physical labor, be the climatic conditions what they may. The latter question, after all, is paramount to the economic conquest of tropical countries, but there enter into it psychological considerations which are only too often ignored. There are the strongest reasons for believing that an infinite amount of mischief has been done by reckless writers on tropical exploration, who have overemphasized climatic disadvantages, attributable to parasitical and insect life with extraordinary dangers of disease. In my own tropical experience, I have never suffered a day's illness, primarily because of the care employed in safeguarding my health against parasitical infections. In numerous instances I have found the accounts of otherwise thoroughly responsible authorities on tropical sections decidedly misleading, as regards matters concerning comfort and health. It, of course, is largely the individual viewpoint that controls personal conclusions, but I am convinced that by a common-sense attitude towards local conditions, however much at variance with those prevailing in northern latitudes, both comfort and health can be maintained in almost any section of the Central American Tropics, as abundantly proven by numerous individual records of tropical residents, which I have personally collected from those with whom I came in contact.

The classical illustration of health progress in the Central American Tropics, is, of course, the Panama Canal Zone. The dramatic aspects of that titanic achievement frequently, however, obscure important results achieved in other sections or localities of Central America, or the West Indies. Foremost among these, I would place the sanitary control of the plantations, or possessions, of the United Fruit Company, which extend to most of the countries at present under consideration. They represent a collective aggregate of experience probably second to none in the tropical world. In a long series of admirable reports, a wealth of information

has been made available to the medical profession by the Medical Department of the United Fruit Company, to which heretofore but inadequate attention has been given. In matters of detail the reports unquestionably could be improved upon, particularly as regards the presentation of the vital facts in a more generally useful form. Those who are concerned with administrative matters frequently overlook questions of the first importance to those who are interested in special phases of developments.

The United Fruit Company in 1923 employed in its tropical possessions 9,651 white persons and 44,986 colored persons, including members of families and non-employees. The Medical Department of the company had supervision over, or direct contact with, 158,213 persons. There were treated in its hospitals during the year 28,398 patients, and in hospital dispensaries 79,462 more. It will be granted that whatever conclusions one may arrive at, the basis therefor is numerically sufficient. Including treatment in field dispensaries, the total number of treatments in hospitals and field dispensaries during the year reached 227,545 and the total number of hospital days 332,399. The number of deaths during the year in hospitals and field dispensaries was 1,086, of which 88 were the deaths of white employees, and 623 the deaths of colored employees. The average daily number of patients in the company's hospitals, including employees, non-employees, and members of families was 910. The company for the year reports a death rate for white employees of 9.12 per thousand, and for colored employees 13.85. Reports of non-employees, including members of employees' families, gave a death rate of 3.1 for whites and 3.9 for colored. The latter figures are probably of somewhat doubtful accuracy. The average number of hospital days per annum per employee was 5.02, and the hospital admission rate per annum per thousand employees, 4.21. The average number of dispensary treatments per employee per annum was 3.48.

The foregoing information is given in detail for each of the 9 principal divisions of the company's operations. Thus, for the white employees, the death rate for the Banes Division of Cuba was 5.47; for the Colombia Division, 6.53; for the Costa Rica Division, 19.19; while in the Guatemala

and Jamaica Divisions no deaths of white employees were reported. For the Panama Division the death rate was 5.15; for the Preston Division of Cuba, 5.64; for the Tela Railroad Division, 6.97; and for the Truxillo Railroad Division, 7.94. None of these rates, except that for Costa Rica, are suggestive of other than normal conditions. A factor which enters into the question, however, is the so-called repatriations, or the return of invalided employees to their homes. The Medical Department gives information on this point, which may be briefly referred to. During the year 1923 the company repatriated 109 employees, most of whom were whites. But, unfortunately, the tabulation does not show the precise division, which, however, may be given later in the form of a footnote. This number is not sufficient to invalidate general conclusions based upon the death rate alone. It would seem well worth-while on the part of the company to initiate a follow-up method, and ascertain the after effects of tropical residence in the case of those who leave the Tropics on account of ill-health.

The medical reports for 1923 contain a wealth of extremely interesting information, which to review on this occasion would unreasonably extend my permissible limitations of time. I cannot omit, however, to quote from the report some observations regarding the employees' death rate, which reached its lowest point, or 8.06 per 1,000, during 1917, and its highest point, or 14.73, during 1919. It would require an exceedingly minute analysis of the causes of illness to determine the reasons for the fluctuations and the true death rate, adjusted for age, sex, color and possibly duration of tropical residence. There is also the question as to whether the records include all the deaths that actually occurred, since in Jamaica this does not seem to be the case. The death rate for Jamaica during 1923 was only 1.52 per 1,000, it being explained that this was due to the fact that "the United Fruit Company does not maintain a hospital in Jamaica and, consequently, a laborer who realizes that he is seriously ill, will leave the service of the company and enter a government hospital." Under such conditions, of course, conflicts in mortality records cannot be avoided. But it is doubtful whether this conclusion applies to any other than the Jamaica Division. Under a new method of calculation,

the deaths of white employees from temperate zones are separately calculated, the death rate for the year 1923, based upon 1,961 employees, having been only 5.1 per 1,000. There were only 10 deaths, of which 4 occurred in the Preston (Cuba) Division, and 2 in the Truxillo Railway Division. These cases are described in full as follows: —

Case 1. Laborer, age 58, born in Spain, resided in Cuba 30 years, pulmonary tuberculosis.

Case 2. Farm superintendant, age 50, born in France, tropical resident period not known, traumatism by railway.

Case 3. Foreman, age 37, born in England, resided in Tropics 3 months, delirium tremens, chronic alcoholism, morphinism, cirrhosis of the liver, acute nephritis, atheroma, ischio-rectal abscess. (Treated only 4 days).

Case 4. Laborer, age 36, born in Spain, resided in Tropics 8 years, acute infection of kidneys.

Case 5. Laborer, age 44, born in Spain, resided in Tropics 24 years, hemoglobinuric fever.

Case 6. Laborer, age 22, born in Spain, resided in Tropics 4 years, traumatism.

Case 7. Laborer, age 33, born in Spain, resided in Tropics 16 years, hemoglobinuric fever.

Case 8. Locomotive engineer, age 44, born in the United States, resided in Tropics 18 months, syphilis (treated 7 days).

Case 9. Contractor, age 35, born in Spain, resided in the Tropics 4 years, bacillary dysentery.

Case 10. Machinist, age 60, born in the United States, resided in the Tropics 2 years, bacillary dysentery.

In the analysis of the causes of mortality it is explained that "malaria was naturally the greatest morbidity in our divisions. It was responsible for 38% of the admissions to our hospitals during 1923, and for the same percentage during the preceding 9-year period." Injuries and other external causes comprised 9% of the hospital cases. Hookworm comprised approximately 5%. The comparative prevalance of the different types of malaria during the past 3 years and during the 9-year period 1914–1922 has been as follows: —

CASES OF MALARIA IN THE EXPERIENCE OF THE UNITED FRUIT COMPANY 1914–1923

	Percent of Total			Average for 9 years	Percent of Deaths to Cases
	1921	1922	1923		
Estivo-autumnal	39.4	27.3	31.1	27.9	1.93
Tertian	25.4	30.2	36.2	27.5	.39
Quartan	1.0	.6	.6	.8	.37
Mixed	3.7	3.6	1.3	3.2	1.18
Clinical	27.7	36.4	28.9	38.4	.76
Cachexia	2.3	1.4	1.2	1.7	5.96
Hemoglobinuric fever	.5	.5	.7	.5	26.64

Another important factor of ill-health in the Tropics is dysentery. The table following gives the death rates per 1,000 employees for the period 1920–1924. Also, the hospital cases and the fatality rate.

DYSENTERY

	Deaths per 1,000 Employees	Hospital Cases 1,000 Employees	Deaths per 1,000 Cases
1920	.64	8.2	78
1921	.54	7.1	76
1922	.91	16.0	57
1923	1.91	23.2	22
1924	.99	13.6	73

I conclude these observations with a brief reference to venereal diseases and cancer. The average hospital admission rate from venereal diseases per 1,000 employees during the 4 years 1920–23, was 31.2, or 3.1%. The death rate was 0.34 per 1,000 and the fatality rate 10.8 per 1,000. A review of the 4 years' records indicates a trend towards a wider distribution, and an increased frequency, as well as an increased mortality rate. Venereal diseases are unquestionably, next to malaria, the chief bane of the Tropics. It is hardly necessary to point out that they prevail chiefly among the colored or native element.

Cancer is relatively infrequent, but during the 4 years under observation the prevailing case rate has been 0.67 per

1,000 employees. The death rate has been 0.25 per 1,000, which would be equivalent to a rate of 25 per 100,000 of population, or approximately ¼ of the rate prevailing in the United States at the present time. As observed by the Medical Director, "Cancer does not seem to play an important role in our morbidity and mortality statistics." This seems to be the general experience in the Tropics outside of large centers of population. The fatality rate in cancer cases was 37%, due, of course, in a large measure, to the probable inoperable condition of the majority of cases, when they finally came for treatment.

Cancer among primitive races has of late attracted a fair measure of attention. There is no more hopeful field for cancer-research than the correct ascertainment of the occurrence of malignant tumors among the different races of mankind, and their intimate relation to the habits, or mode of living of those concerned. Experience has shown that in large centers of population in the Tropics the cancer death rate is about as high as in the large centers of population in the non-Tropics. Havana, Cuba, has a very high cancer death rate, although the rate for the Island as a whole, is not excessive. It is to be hoped that this conference will concern itself seriously with certain aspects of the cancer problem under tropical conditions.

It has been said by Professor Ward, of Harvard, with regard to climates, that:

> The acclimatization of the white race in the Tropics is a question of vast importance, and upon it depend the control of government and the utilization of the Tropics. It is a very complex problem and has been much discussed. It is complicated by the controls exercised by race, diet, occupations, habits of life, and the like.

Of the foregoing elements, diet is probably one of the most modifying factors. The dietary habits of native races have not, unfortunately, been as thoroughly studied as would be required for a definite conclusion. Most white residents in tropical regions live, to a considerable extent, upon imported and canned foods, which tend to duplicate conditions of life common to the countries from which they came. If there is more or less trend towards certain diseases and certain dietary habits, it would only be natural to

expect that the mortality rates in the course of time, should conform to each other. With regard to no disease is this matter of greater importance than with regard to cancer.

The most impressive illustration of sanitary progress in the Tropics is the Panama Canal Zone experience. Most of the prevailing views, however, rest upon the earlier experience covering the period of construction, which, in many respects, have been improved upon in recent years, and in directions well deserving of consideration. The Panama Canal Zone has, from the outset of the American occupation, been fortunate in its sanitary officers, including such highly honored names as those of Major General Gorgas. Work has been carried forward by his successors with admirable consistency of purpose, to make the Panama Canal Zone a model for the tropical world. The Annual Reports of the Health Department contain a wealth of useful information, not only to the student of mortality statistics, but particularly to the sanitary officer anxious to model his own activities along the lines of what is generally conceded to be acceptable practice for tropical regions, with a special regard to the health and longevity of a small, resident,white population. For the present purpose it will be sufficient to deal with the population in the aggregate, but, as occasion may require, differentiate employees and non-employees. It is hardly necessary to point out that the cities of Panama and Cristobal, while outside of the Panama Canal Zone, are both, by treaty, under the sanitary administration of the American Government. References to the Canal Zone, however, do not include the two cities, which are separately considered in the annual reports.

It may be pointed out that the employees of the Panama Canal and the Panama Railway during the year 1922 numbered 10,447, as compared with 30,673 for 1920. Since the completion of the Canal, the number of employees has gradually been reduced, but a minimum has probably now been reached. The latest report available is for the year 1922. In that year the total death rate of employees was 6.89 per 1,000, compared with 6.46 in 1921, and 8.70 in 1920. The death rate from accidents or casualties has always been very high in the Canal Zone, partly on account of the large amount of mechanical equipment. The death rate from

disease alone, therefore, was only 6.13 per 1,000, as compared with 5.70 in 1921 and 7.40 in 1920. These death rates may be accepted as a sufficient indication that the health progress of the Zone attained under Major General Gorgas has been successfully continued to the present time. It may be said, in this connection, that the present Chief Health Officer is Colonel H. C. Fisher, of the United States Army, while the Chief Health Officer of Panama City, is Dr. Henry Goldwaite, and at Cristobal, Dr. Jesse L. Bird.

The death rate for the Canal Zone for the total population — or employees and non-employees — numbering in 1922 some 31,000 was 8.17. This compares, or contrasts with a rate of 10.91 during 1916, and a maximum rate of 49.86 during 1906, when preliminary construction was most actively in progress. The maximum population of the Zone was reached by 1911, or 90,434, among whom there occurred 1,385 deaths, or at the rate of 15.32 per 1,000. The death rate for 1922 is, therefore, the lowest on record, with the exception of the 2 years 1920–1921.

The population of Panama City is estimated at about 60,000. The death rate in 1922 was 21.29 per 1,000, or the lowest on record, with the exception of the year 1919. The death rate was as high as 65.82 per 1,000 in 1905, and 44.75 per 1,000 in 1906. It had decreased to 31.95 per 1,000 by 1913, and to 28.08 per 1,000 in 1917. Subsequent to that year it has been between 22 and 21 per 1,000.

The death rate for Panama City is necessarily increased by unsatisfactory conditions, and a considerable amount of population congestion. It must further be considered that the population consists almost entirely of negroes, or Panamanian mixed-bloods, with a small proportion of pure-blooded Indians, usually of the San Blas Tribe. The population of Colon, on the Atlantic side of the Isthmus is 31,393. The death rate reached a maximum of 51.43 per 1,000 in 1906, but it fell to 26.32 during 1908, and maintained a level of about 22 to 23 during the intervening years, until the lowest rate on record was reached in 1922, the rate for 1921 having been 17.26.

The outstanding disease on the Isthmus is malaria and, regardless of the most strenuous efforts at the eradication of the disease, it continues in a mild form and affects a con-

siderable proportion of the population. The malaria admission rate among the employees of the Panama Canal Zone rose very rapidly between 1904 and 1906, or from 125 to 821 per 1,000. It was then that the first efforts of Major-General Gorgas, acting upon the suggestions of Sir Ronald Ross, became effective and the rate was reduced during the following year to 424, and the year after to 282, with a continuous decline during the years following, until 1919, when there was a rise, from a minimum of 14 per 1,000 (in 1917) to 31 per 1,000 (1919). In 1920 the rate was 19, in 1921 it was 15, and in 1922 it was 17 per 1,000. The mortality from malaria reached a maximum in 1906, when the rate was 7.45 per 1,000. It fell during the year following to 3.51, the next year to 1.37, and by 1913 to 0.30 per 1,000. Subsequent thereto, the rate rarely exceeded 10 per 1,000, but a rate of 15 was reached by 1920, and *there were no deaths from malaria among the employees during 1921 and 1922.*

In the combined area of the Canal Zone and the cities of Panama and Colon, the malaria mortality rate has fallen from a maximum of 9.49 per 1,000 in 1906, to 0.21 in 1916 and 0.15 in 1922. Thus, the malaria danger, while not extinct, is nevertheless one of a decidedly lesser degree of seriousness than during even the recent past, while in contrast to the early period of construction the conditions now are those of a thoroughly modern community, in which conditions of life are not incompatible with good health and the attainment of normal longevity.

Of course, the fact must not be overlooked that the Panama Canal Zone population represents, in part at least, a selected body of people, who are living, in many respects, under ideal conditions, receiving substantial wages and are in a position to obtain nourishing food and adequate shelter.

It had been my intention to discuss in some detail the mortality experience in the Panama Canal Zone by specified causes, but this would carry me too far on the present occasion. Certain facts, however, may be briefly stated to advantage: —

Among the residents of the Panama Canal Zone and the cities of Panama and Colon, there occurred, during 1922, 1,978 deaths from all causes, of which 268 were the deaths of white persons, 685 of blacks, and 25 of Orientals. Among

the total population, irrespective of race or sex, there occurred 5 deaths from typhoid fever, 18 deaths from malaria, 7 deaths from amoebic dysentery, 7 deaths from bacillary dysentery, 5 deaths from leprosy, 18 deaths from pellagra, 2 deaths from beri-beri, 2,841 deaths from pulmonary tuberculosis, 42 deaths from different forms of syphilis, 74 deaths from cancer, 7 deaths from diabetes, 2 deaths from acute yellow atrophy of the liver, 22 deaths from cirrhosis of the liver, 144 deaths from Bright's disease, and 4 deaths from puerperal septicemia. There were 15 deaths from suicide, 55 deaths from accidents, and 9 deaths from homicide.

This analysis does not indicate very conclusive evidences of tropical effects on the mortality, which, with few exceptions, conforms to the corresponding record for our southern states. It should perhaps have been said that pneumonia caused a considerable mortality, — or, specifically, there were 21 deaths from pneumonia unqualified, and 83 deaths from lobar pneumonia, with 7 deaths from pleurisy. From a practical point of view, both tubercular and non-tubercular respiratory diseases are the most serious health problems among the adult population in the Canal Zone.

I am able to add to the foregoing a very brief analysis of the essential facts concerning the causes of death of white employees on the Isthmus since 1914. For this information I am sincerely obliged to Colonel H. C. Fisher, Chief Health Officer of the Panama Canal Zone, who has been good enough to have the data compiled for me. It was at my suggestion that this information was first collected and incorporated in the monthly reports of the Panama Health Department and was published in this form for a number of years until, for some reason or other, it was discontinued. In place of an extended discussion, I give the actual facts, as they have been reported to me, eliminating, however, deaths from accidents, suicide or homicide, as not bearing upon the problem of acclimatization or tropical residence. It may be said, however, in this connection, that during the period of construction the number of deaths from accidents was always extremely high, and it is only during very recent years that the rate has been reduced to more normal proportions. Since 1914 there have been 52 deaths from accidents in a mortality of 150 from all causes.

CAUSES OF DEATHS OF WHITE AMERICAN EMPLOYEES ARRANGED WITH REFERENCE TO AGE AND LENGTH OF RESIDENCE ON ISTHMUS

From January 1, 1914, to December 31, 1923

Date of Death	Cause of Death	Age	Length of Residence on Isthmus
Mar. 10, '14	Aneurysm	34	7 yrs.
Mar. 19, '14	Apoplexy	41	5 yrs.
Mar. 31, '14	Carbuncle of face	25	4 yrs.
Apr. 1, '14	Encephalitis	38	7 yrs.
Apr. 8, '14	Chronic nephritis	52	4 yrs.
May 21, '14	Acute nephritis	44	3 mos.
July 17, '14	Apoplexy	64	2 mos.
Aug. 3, '14	Cholecystitis	35	3 mos.
Sept. 12, '14	Tetanus	42	9 yrs.
Aug. 12, '14	Organic disease of the heart	34	7 yrs.
Sept. 13, '14	Broncho pneumonia	63	4 yrs. 8 mos.
Aug. 22, '14	Acute nephritis	42	8 yrs.
Sept. 30, '14	Organic disease of the heart	36	8 yrs.
Nov. 12, '14	Purulent infection	38	5 yrs. 6 mos.
Jan. 6, '15	Malaria	24	2 yrs. 6 mos.
Jan. 24, '15	Malaria	68	23 yrs.
Feb. 17, '15	Acute alcoholism	45	10 yrs.
Apr. 5, '15	Carbuncle	48	3 yrs.
Apr. 6, '15	Cancer of liver	58	6 yrs.
July 8, '15	Acute intestinal obstruction	40	6 yrs. 4 mos.
Aug. 2, '15	Pneumonia, lobar	43	7 mos.
Aug. 6, '15	Alcoholism, acute	30	10 yrs.
Oct. 11, '15	Senility	75	10 yrs.
Dec. 6, '15	Duodenal ulcer	38	2 yrs. 8 mos.
Jan. 10, '16	General peritonitis	37	8 yrs.
Mar. 15, '16	Disseminated tuberculosis	31	1 yr. 6 mos.
Mar. 16, '16	Disease of the intestines	51	1 yr. 4 mos.
Mar. 27, '16	Chronic nephritis	51	35 yrs.
July 25, '16	Alcoholism	45	9 yrs.
Dec. 5, '16	Aneurysm, aortic	38	10 yrs.
Jan. 14, '17	Pulmonary hemorrhage	53	11 yrs.
Jan. 18, '17	Septicemia and pyemia	44	1 yr.
Jan. 20, '17	Chronic alcoholism	44	?
Mar. 1, '17	Gangrenous pancreatitis	30	6 yrs.
Mar. 3, '17	Endocarditis	29	4 yrs.
May 17, '17	Chronic nephritis	65	10 yrs.
June 27, '17	Anaemia, secondary	39	7 mos.
June 27, '17	Toxaemia, following thyroidectomy	25	9 yrs.
July 10, '17	Streptococcus meningitis	42	4 yrs.

CAUSES OF DEATHS OF WHITE AMERICAN EMPLOYEES ARRANGED WITH REFERENCE TO AGE AND LENGTH OF RESIDENCE ON ISTHMUS. — *Continued.*

From January 1, 1914, to December 31, 1923.

Date of Death	Cause of Death	Age	Length of Residence on Isthmus	
July 10, '17	Aneurysm, aortic	48	12 yrs.	
Aug. 23, '17	Chronic nephritis	37	9 yrs.	
Sept. 8, '17	Cancer, general	46	12 yrs.	
Sept. 11, '17	Organic disease of the heart	40	6 yrs.	
Sept. 13, '17	Chronic nephritis	57	14 yrs.	
Oct. 16, '17	Acute nephritis	54	12 yrs.	
Oct. 31, '17	Chronic nephritis	65	10 yrs.	
Nov. 3, '17	Arterio sclerosis	63	12 yrs.	
Nov. 7, '17	Cancer of the stomach	67	6 yrs.	
Jan. 5, '18	Chronic nephritis	39	12 yrs.	
Jan. 11, '18	Organic disease of the heart	43	4 yrs.	6 mos.
Feb. 21, '18	Septicemia	41	9 yrs.	
Feb. 25, '18	Organic disease of the heart	33		9 dys.
Mar. 26, '18	Apoplexy	63	13 yrs.	
Apr. 2, '18	Organic disease of the heart	42	5 yrs.	
July 14, '18	Diabetes	47	?	
Apr. 16, '19	Organic disease of the heart	39	13 yrs.	
June 18, '19	Pneumonia, lobar	39	18 yrs.	
Sept. 30, '19	Sinusitis, purulent	25	4 yrs.	
Nov. 23, '19	Syphilis	67	?	
Mar. 5, '20	Chronic nephritis	45	4 yrs.	
Mar. 19, '20	Apoplexy	46	8 yrs.	
Mar. 24, '20	Influenza	26	2 yrs.	
Apr. 5, '20	Influenza	38	10 yrs.	
June 18, '20	Strangulated hernia	46	7 yrs.	
June 29, '20	Appendicitis	47	12 yrs	
Aug. 27, '20	Malaria, pernicious	45	13 yrs.	
Sept. 1, '20	Pneumonia, lobar	33	5 yrs.	
Sept. 8, '20	Gangrenous appendicitis	37	12 yrs.	
Oct. 8, '20	Malaria	33	7 yrs.	
Oct. 10, '20	Cancer of rectum	54	11 yrs.	
Dec. 5, '20	Broncho-pneumonia	27	1 yr.	
Jan. 10, '21	Cancer, small intestine	43	10 yrs.	
Feb. 16, '21	Brain tumor	39	5 yrs.	
Apr. 2, '21	Ruptured duodenal	48	4 yrs.	
Apr. 14, '21	Endocarditis	46	16 yrs.	
Apr. 26, '21	Arterio-sclerosis	57	15 yrs.	
July 2, '21	Typhoid fever	44	9 yrs.	
Sept. 3, '21	Chronic nephritis	56	15 yrs.	

CAUSES OF DEATHS OF WHITE AMERICAN EMPLOYEES ARRANGED WITH REFERENCE TO AGE AND LENGTH OF RESIDENCE ON ISTHMUS. — *Continued.*

From January 1, 1914, to December 31, 1923

Date of Death	Cause of Death	Age	Length of Residence on Isthmus
Sept. 6, '21	Apoplexy	73	1 yr. 2 mos.
Feb. 5, '22	Apoplexy	46	12 yrs.
Mar. 22, '22	Ruptured duodenal ulcer	40	15 yrs.
Apr. 12, '22	Embolism and thrombosis	36	8 yrs.
July 20, '22	Cancer of the lung	53	15 yrs.
July 22, '22	Syphilis, tertiary	60	18 yrs.
Dec. 3, '22	Cancer of intestines	46	16 yrs.
Dec. 18, '22	Cancer of kidney	51	11 yrs.
Jan. 12, '23	Gastric hemorrhage	69	14 yrs.
Jan. 16, '23	Malaria	63	?
Jan. 23, '23	Organic heart disease	59	18 yrs.
Jan. 30, '23	Apoplexy	59	17 yrs.
Feb. 2, '23	Organic heart disease	43	?
Mar. 9, '23	Cancer of stomach	47	16 yrs.
Mar. 10, '23	Tuberculosis of the lungs	53	18 yrs.
June 3, '23	Purulent meningitis	45	12 yrs.
July 2, '23	Tuberculosis of the lungs	62	4 yrs.
Oct. 17, '23	Organic disease of the heart	54	?
Nov. 25, '23	Broncho-pneumonia	51	19 yrs.
Dec. 30, '23	Softening of the brain	66	?
		4,522	806
		46.1	9.4

A review of this mortality experience conclusively proves the relative infrequency of typical tropical affections. Practically every disease is represented, but during recent years malaria and dysentery have been of no serious importance. The average age at death, of those dying from disease, was 46.1 years; and the average length of residence, for those reporting the time and the duration of residence, was 9.4 years. The length of residence tends to increase and in one case, at least, the employee had been 35 years on the Isthmus, dying from chronic nephritis. There was another case of 23 years' residence on the Isthmus, death being caused by malaria, — but this was as far back as 1915.

It would seem to me that the foregoing may safely be accepted as conclusive evidence that the strictly tropical affections on the Isthmus of Panama are no longer a matter of serious concern to those who adopt reasonably satisfactory precautions and habits of life conducive to health and longevity.

It had been my intention to deal in some detail with the mortality experience of other countries of Central America and the islands of the West Indies, but I think the foregoing evidence is sufficient for the purpose of emphasizing the conclusion that the dangers and disadvantages of life in the Tropics are now largely a thing of the past. Just as in the northern regions precautions are always necessary against sudden weather changes, or extremes of cold, so likewise in the Tropics there will always be need of reasonable precautions in the matter of sanitation and exceptional care as regards correct habits of living. In the light of my own experience and investigations, extending over many years and including numerous visits to tropical regions, I feel satisfied that the attainment of normal longevity is not difficult, provided the person concerned maintains industrious habits and keeps steadily and properly at work. Idleness in the Tropics is a besetting sin of a large number of both whites and natives, and idleness breeds discontent, as well as disease.

In the second place, there must be considerable restraint as regards indulgence in intoxicating liquors, which, if drunk to excess, are productive of even greater mischief in the Tropics than in northern latitudes.

In the third place, there must be absolute avoidance of the contraction of venereal diseases, which, in the Tropics are a source of infinite mischief and the true cause of many premature deaths, which might otherwise have been prevented.

Fourthly, every effort must be made to avoid parasitical infections, particularly hookworm and malaria. The more strictly tropical diseases very rarely affect the white race — and then, as a rule, only if the whites are in very intimate contact with the natives.

It is my deliberate judgment that the Tropics are a fruitful field for development on the part of the white race, and that such development is an imperative duty, called for by

the highest consideration of public policy. Enormous areas now lie practically idle, which would afford a proper means of sustenance to countless thousands who now live under atrocious conditions of life in the crowded centers of Europe. The native element requires consideration and a reasonable measure of control. It is as yet far from economically efficient, as it could be made, if free from the three undermining causes of ill-health: that is, venereal diseases, hookworm, and malaria. Free from these evils, the natives are an excellent labor element, capable of a very much larger measure of development.

In this respect, once more a tribute must be paid to the United Fruit Company for what it has done to improve the economic condition of the native people, who, to so large an extent, represent its labor force in the Central American Tropics. Where so much has been achieved, it is a foregone conclusion that merely the beginning has been made, and that the outlook for the future is one of great promise, but it is of the first importance that false conceptions regarding tropical health should be done away with, and that there should prevail a rational understanding as to the conditions under which health and long life are not inconsistent with prolonged residence in southern latitudes.

Since this was written I have read with much interest the really remarkable address on "The Influence of Tropical Climate on Man," by Dr. C. Eijkman, Professor of Hygiene of the University of Utrecht (*The Lancet*, May 3, 1924). This address is a most helpful presentation of all the essential facts involved in the present discussion, interpreted in the light of practical experience in the East Indies. I could not possibly hope to discuss this paper without recasting my own presentation of certain mortality facts for the West Indies, but I may quote some of the concluding sentences in part as follows: —

> The question whether the colonization of whites in the Tropics is possible, in the full sense of the term, is not one of a purely hygienic nature. Let us leave alone for a moment the great variety of factors which come into play here, and let us see what more experience teaches. For more than three centuries there has been a continuous stream of thousands, and hundreds of thousands, of people going from Europe to oversea lands to

which Portuguese and Spaniards have shown the way. And the result? Everywhere outside the Torrid Zone, and in the countries bordering it, wherever summer and winter alternate, in North America, South America, South Australia, Tasmania, and New Zealand, we see the white race, braving all dangers and difficulties, gain a firm foothold, pressing back the native, supplanting him.

How different in the hot regions! The thoroughbred white man attains nowhere any further than to an aristocratic minority. Wherever things seem otherwise, as in the lowlands of Mexico, in some West and East Indian Islands, it is not they and their pure descendants who form the real nucleus of the population, but a more or less coloured people, the product of cross-breeding, who here and there, as Réclus has it, by a "complaisance du Fisque" have undergone a "blanchissement officiel." Now I do not wish to argue that the mere fact of unmixed white colonies not thriving anywhere in a tropical climate, is a proof that for purely sanitary reasons there is no possibility of their so doing. For, indeed, if the viability of the white race in the Tropics remained unimpaired, yet the pure-blood propagation in following generations would be more than an exception, with the manifold opportunities for the mingling of the races. One might, for instance, argue with the same justice that Germans, in the long run, cannot stand the climate here, because, notwithstanding the many immigrants, nowhere in this country has a German colony come into being. Possibly, too, the special aptitude of Jews for colonization is not so much due to natural causes as to the traditional custom of keeping their race pure and not allowing it to disappear in the multitude. But it cannot be denied that, whereas the white races dominate nearly everywhere in the Temperate Zone, in the Tropics they get no further than a numerical minority, and this proves at any rate that the native race can engage with much more success in the struggle for life — that, therefore, the superiority of the white race is only a relative one. Indeed, where the native population was thin-sown, it has been necessary to import men from elsewhere, negroes, Indian coolies, proof against hard toil in the hot climate, to supply the urgent need of labor.

However plausible this argument may sound, it is not conclusive. It fails, in the first place, to emphasize the terrific population-pressure of a vast number of natives against a small remnant of foreign-born whites. Conditions today are different from generations ago, when the ruthless

extermination of natives was frequently the first step in successful colonization. The peaceful assimilation of native races and their direction and control by foreign-born whites, rest today everywhere upon humane considerations of public policy. Hence only a few emigrate to the tropical zone, and those largely for purposes of discharging executive and supervisory functions. In the East and West Indies are generations of pure-blood white people who have maintained themselves to a fair degree. On account of more attractive possibilities, social or economic, in the Temperate Zone, there is a constant loss by emigration, which is frequently not made good by immigration.

Dr. Eijkman, himself, points out that the old notions formed about the processes of acclimatization have not been confirmed by direct investigation. He considered the chief objectively perceptible difference between the two races to consist in the function of the skin. But as to what it really is that makes the heat so exhausting, we are far from apprehending. But if this is the chief difference, it must be self-evident that it cannot form an insuperable bar to successful adaptation.

It is my judgment that with the gradual elimination of parasitical diseases, and a more rational diet on the part of foreign born residents of tropical countries, the difficulties of successful acclimatization will largely disappear. For Dr. Eijkman, himself, does not point out, after painstaking experiments and observations, that there are really far-reaching differences in metabolism and heat-regulation which might bear upon comparative physiology and pathology. In fact, he observes that "taking into account the individual fluctuations among the same race, we may conclude that there is no perceptible difference between the two races in the number of sweat glands." He remarks also that the white man in the Tropics sweats more plentifully and, therefore, secretes more bodily fluids, so that his kidneys show greater activity, independent, to a great extent, of the water intake. All that he has to say upon these matters is deserving of most thoughtful consideration.

In reply to the question as to whether, in the far-off future, under possibly quite different circumstances, the conditions for colonization may become more favorable, it is said "it

does not seem at all unlikely, for technical skill and industry backed by science, stick at nothing where there is a question of assisting man in the struggle for life. If he cannot be made fit for the climate they make the climate fit for him."

This is precisely the viewpoint which underlies the medical work of the United Fruit Company. It aims persistently at making conditions favorable to life and health, more in harmony with the need of the different types of mankind for the care of which it is responsible. It is without question the most promising, as well as successful, experiment of its kind on record, and it is to be hoped that much more information than has heretofore been published will, in the future, become available, to emphasize the effect of the white man's adaptation to tropical conditions of life. The Company provides work for those who are willing to labor. It provides amusement and recreation, otherwise, for the proper use of leisure time; it provides medical attention for those who are ill, even in the earlier stages of diseases; and it provides as nearly as possible the required sanitary improvement, as a safeguard against needless parasitical infections. It supervises the food supply in many directions, while it aids in the health-education of the people in various forms.

Of course more could be done, and no doubt more will be done, in the light of subsequent experience. The Company encourages research, on a broad scale, both of an economic and of medical nature. On the whole, the housing conditions of the labor element are satisfactory. Water-supplies are carefully supervised. Various and close contacts with the outside world are maintained through an admirable system of wireless telegraph. Hence there is not the monotony which is so often a deathly influence in remote tropical regions. There is frequent communication with the outside world, and those who are ill and in need of a climatic change are without difficulty transported back to their homes. Under such conditions tropical acclimatization should not be difficult, and I believe that, in a general way, it may be said that the large majority of the Company's employees are entirely satisfied with their tropical surroundings. Anyone who is familiar with long-time residents in the Panama Canal Zone, knows how firmly attached such residents are to the

Isthmus. In many cases those who have lived on the Isthmus and returned home, continue to long for a return.

In the light of my own experience, the fundamental question involved is one of individual adaptation. There are types of mankind who, for one reason or another, have no place in the Tropics. Medical science should attempt more precisely to define the types ill-adapted to prolonged tropical residence and continuous heat-exposure. On the other hand, there are types that are admirably suited for tropical development, and they incur no particular risk by even prolonged residence in tropical countries.

In its final analysis it is essentially a question of common sense and rigorous discipline in matters of personal habits, and a proper vocational pursuit yielding a sufficient income for the higher needs of life.

DISCUSSION

Sir Thomas Oliver (Opening the Discussion). — I had hoped that some one more capable than I would have been called upon to introduce this discussion. We have listened this afternoon to an address of a high character.

Some of us were not a little astonished when Dr. Hoffman told us that many of the diseases which we regard as tropical today are really not tropical at all, and he based that remark upon this fact, among other things, — that yellow fever, years ago, was not confined to this particular part of the world, but was present as far north in the United States as Boston. That circumstance recalls to my own mind the fact that a few decades ago, even in far-away Great Britain, we had malaria, a common disease in the fen districts of England; and at one time, too, we had leprosy and lepers' houses in Scotland. It is not more than 100 or 120 years ago since the last indigenous case of leprosy disappeared from Scotland.

Dr. Hoffman stressed, and properly so, the fact that of all the diseases requiring to be eradicated for man and for his work in the Tropics, malaria is the most important, because it is the most prevalent and the most persistent. The Congress is, I think, at one with him on this point. He alluded to the fact that in Cuba, a few years ago, living conditions were practically impossible for the white man. I can point to an instance that is well known to most of you, — namely the Gold Coast of West Africa, which until recently, was regarded as the white man's grave. There, conditions today are so much improved that men from my own country do not hesitate to go to the Gold Coast, for they feel that with care

life can be lived there with as good chances of enjoying normal health as at home.

Dr. Hoffman spoke of the problem of the Tropics as one of the white man adapting himself to his environment. I stand with Dr. Hoffman in his advocation of man trying, wherever he is placed, to improve his environment as regards health, for if he will put into practice the results of knowledge and experience, many of the diseases which are so deadly today will gradually diminish or disappear.

The reader of the paper referred to the inefficiency of native labor, and he pointed out that the physical defects are due not only to climatic conditions, but to imperfect feeding and the lack of sanitation in which the natives have to spend their life. He made the remark that thousands of lives have been lost as a result of unsuitable dressing, imperfect feeding, and bad housing. It is a sad thing, no doubt, that thousands — and millions — of lives should through the centuries have been lost through carelessness, but, after all, is not the history of the world one long-drawn-out story of stupidity of man in his struggle for selfish and national ends.

The requirements of public health should be insisted upon and their advantages pointed out to all. If men or business companies are going to exploit the Tropics, they should certainly carry to the people there the blessings of public health and hygiene. Companies and men cannot come to these parts of the world unless they are prepared to give the natives all the advantages of civilization enjoyed by themselves.

The reader of the paper also touched upon the question of the consumption of alcohol in the Tropics; in his opinion the use of a moderate amount of alcohol, just as in the temperate zone, is not followed by serious results. It is the excessive use of alcohol that must be stopped.

I agree with Dr. Hoffman when he says that what we have seen on this Island convinces us that unless the Government of this island will do more to assist it than it has done in the past, Jamaica will not be the healthful place it ought to be. Much can be done in this direction by government and municipal authorities; also by medical men who are interested in these problems, and who are prepared to devote time and give careful study to these questions, so as to devise means for the elimination of the diseases now prevalent on the Island, by putting preventive measures into operation.

Dr. Hoffman has given us the benefit, not only of his wide academic experience of the subject, but also of his practical knowledge of the situation, gained during his visits to the Tropics. I am but voicing your opinions when I say how grateful we are to him for his address.

Colonel Bailey K. Ashford. — My only excuse for speaking is that I have lived the best part of 25 years in the Tropics, and have done some continuous work there; also, because I am a member of a board of medical officers of the Army, to render a report, after four years' observation, of the effect of tropical climate as affecting our American officers serving in Porto Rico with the regiment stationed there. I am now engaged in this work. I would like to consider this question from several points of view.

1. Up to the present time, I think we have not spoken of the mental attitude toward the Tropics, on the part of temporary residents who visit us from the North. In the North there is a chronic fear of the Tropics, and I think we carry that fear to the Tropics with us.

2. Another point is our mental or spiritual incapacity to adapt ourselves to the environment. There are people who come to the Tropics who are unhappy because they cannot see the land they visit turned into a cheap imitation of the particular place from which they come, and they fret themselves almost sick over this. There are northern people who live in the Tropics, and who never know the soul of the Tropics, because they cannot learn the language spoken there. They often take no trouble to study it.

3. Another important thing is nostalgia. — A large number of people are constantly dreaming of home. For that reason, I think, we can really say that a man from the North should have a change of environment every 2 years, if only for a brief period.

4. I think we are all convinced that the food we eat has a great deal to do with our well-being in the hot zone. We must provide more highly cultivated and diverse garden products in the Tropics, because today it is almost impossible to get the kind of fresh food we should eat.

5. The next thing is rest. The native laborer of the Tropics works "in low" (if I may compare the human machine to the popular modern product, the automobile) and the American, from the moment he disembarks in the Tropics, goes right into "high" and stays there until he breaks down. One should be very careful to rest sufficiently to repair the damage of the day, but unfortunately Nature throws most of her charm into the tropical nights, and people are apt to stay up until they are so weary that they are compelled to go to bed.

6. The question of exercise in the Tropics I believe is a very important one indeed. Our regiment is recruited from the native population, and we have to accept somewhat under-nourished recruits, if they have no organic disease. It is marvelous to see the effect of well-directed and well-controlled exercise upon those men.

They become sturdy. A certain amount of exercise is necessary in the Tropics, but very few people ever think of it. I had a good opportunity to see the effect of exercise upon some young civilians who attended a military training-camp in Mayagüez. Of about 100 of these men, all native to the soil, the average weight was around 103 pounds, and in 3 weeks these same men had gained an average of 4½ pounds, from a combination of rest and exercise.

Let us now look at the other side of the page.

7. I believe, personally, that heat and humidity have a deleterious effect upon people from the North, though not so much as has been painted. I think I have seen, among people who otherwise seemed well, that heat and humidity acted deleteriously. It is in *function*, not in the histopathologic laboratory, that we see the effect of the Tropics. The blood pressure falls; there is undoubtedly a retention of nitrogen in the blood. As I mentioned the other day, endocrines are a very dangerous subject, but I believe that whatever the effect of light, or humidity, or heat, may be, there is a decreased functioning in some of our endocrines, especially in the adrenals, and often an aberrant function of the ovary. There is often also a slight fall in the hemoglobin.

8. On the other side lies the great question of the development of children. All of us who have had children in the Tropics know, or at least I think most of us do, that children should go to the North while they are growing.

9. As to diseases, I really believe that the Tropics in which we are living — Porto Rico, Cuba, etc. — are less fearsome from the standpoint of disease, given a fair sanitary service, than the North. Scarlet fever and erysipelas, if they exist at all in the Tropics, are positively less frequent. Gout and real rheumatism are certainly less frequent. Diseases of the kidney seem not as frequent in the Tropics as they are in the North. Diseases of the heart and diseases of the lungs — provided the bacillus of tuberculosis and the pneumococcus do not enter on the scene — are less frequent than in the North. Insanity and mental and nervous diseases, however, are as frequent. Skin diseases are more frequent. The hair is favorably affected, I believe. Complexion depends largely on what one eats, but almost as much on exercise.

10. In conclusion, I should say that tropical climate is a much more negligible factor than we used to think it was. In Panama, for example, the residents live as happily and as healthily as they could in the North, and when we invoke the Canal Zone we certainly chase away the climate bogey. There, in spite of the rent we made in the side of Nature, she smiles most benignly upon us.

I wish to congratulate Dr. Hoffman upon his interesting paper.

Dr. W. E. Deeks. — I believe that adults can live and remain in a healthy condition in the Tropics, and that their children can be happy and develop properly, physically and mentally, provided that they are familiar with the conditions which cause disease, know the methods of prevention, and properly apply them. People going from northern climates to the Tropics should adapt themselves to conditions existing there. As far as possible, they should avoid the use of canned foods, with which they are familiar in the North, and cultivate and learn to properly prepare and eat the vegetables and fruit which grow naturally in the Tropics. It is merely a question of an adjustment of themselves to the new conditions.

Dr. Henry Rose Carter. — When we speak of the Tropics, we nearly always speak of the Tropics of our English brothers, — the wet, continental Tropics. In America it is fair to say that there are 3 kinds of Tropics: — (1) the wet, continental Tropics, of which Panama and Port Limon are types; (2) the insular Tropics, of which this is a fair example, as well as Cuba, Porto Rico, and the Bahamas; and (3) the dry Tropics, say from the southern border of Ecuador, down almost to Cape Horn, where it is as dry as it possibly can be, where hot, — a climate almost like that of Arizona.

Then there is the plateau of high Tropics, including part of Mexico, Central America, the great plateau of northern South America including Caracas, Bogotá, and the Andean plateau to the east of the great plane of Peru. This last is not tropical in climate, in that it is never hot, or only rarely so, and is not to be considered.

We usually mean the wet, or continental, Tropics when we speak of the Tropics, because that is the type of which the white man usually treats — the Gold Coast, the Slave Coast, Panama, Central America, and Mexico. It is not worth while to go into a discussion of all the infectious diseases which exist in the Tropics. If one goes there, he may contract hookworm, malaria, dysentery, etc., but they should not be there. I prefer to lay stress on one thing — and that is, physical exercise. My best friend (one I admire greatly) and I often discussed the question as to whether exercise was advisable in the Tropics. He always assured me that 4 men who had been associated with him had always taken exercise while in that region, and then died, while he took no exercise — and lived.

I always feel better myself, in the Tropics, however, if I do take a certain amount of exercise. I think that exercise is absolutely necessary for healthful living there, and I think the lack of it is one of the main causes of ill health. This question was brought

up before the American Tropical Society, in Washington, by Chamberlain, Vedder, and 2 other men from the Philippines, and they agreed that exercise is a necessity in the Tropics, if health is to be maintained.

In the Canal Zone we found that the stenographers, teachers, nurses, etc., kept well, but that the housewives were in the hospital or complaining of being ill most of the time, because they did not do a blessed thing. Labor in the Tropics is more disagreeable than in the temperate zone. They made their soldiers exercise and we paid our employes to work, and both kept well; but the women who did not work were often sick. It seems to me that exercise is the crux of the matter, and the next is alcohol.

I do not think that use of alcohol is any more injurious in the Tropics than it is elsewhere, but when Americans go there — and the same, I found, was true of the English in South America — they go to places where there is no public opinion, get drunk as a blind owl, and no one thinks anything about it. They go to places where there is very little amusement, and naturally they feel better when they have something to drink.

In Peru, where a great deal of work is being done, I think 67% of the Americans are knocked out by alcohol, and 32% of the English. The same amount would have knocked them out at home, but with other things to do, and with public opinion restraining them, they would not drink so much at home.

My advice to those going to the Tropics is, Take all the exercise you can and as little whiskey.

Sir Arthur Newsholme. — I am sorry that I am not able to contribute any facts to the discussion of this very important subject. I admired very much the customary thoroughness with which Dr. Hoffman prepared his statement. He made clear, I think, his conclusion that the Tropics are not necessarily injurious to the white man, and I think that with that general proposition we should all of us agree. I shall look forward to reading Dr. Hoffman's paper *in extenso*, and I am quite confident that it will be as valuable as the other contributions he has made in the cause of preventive medicine.

Dr. Frederick L. Hoffman (*Closing the Discussion of His Own Paper*). — Of course, when we speak of the Tropics regarding sanitation and health, we generally mean the humid low lands. Any one who has been in the highlands of Peru, Bolivia, and other countries of Central and South America, knows that they are just about as free from tropical diseases as any other highlands. The effects of tropical conditions, therefore, chiefly concern the low-lying regions.

Dr. Carter has referred to the effect of loneliness. It is a most depressing thing in the wilderness, — for instance, in the regions of the upper Amazon — to meet with absolutely nothing that resembles our civilization. There are no telephones, telegraphs, or newspapers except possibly weeks or months old. There is simply little else to do than work, drink, and gamble.

Colonel Ashford has spoken of the psychological attitude of northern residents towards the Tropics. That attitude is due largely to the malign accounts many explorers have rendered regarding tropical regions. They seem to revel in emphasizing the dangers from insects or savage beasts, and of heat. They give gross exaggerations of individual experiences. They are not concerned with the normal experiences of everyday living. Colonel Ashford referred to the value of a change of air. We need to get a change of air in northern countries just as we need it in southern countries.

It has been said that fatigue is really due, not to over-exertion, but to lack of interest. So long as we are interested in our work, we are never really tired. I therefore agree entirely that the psychology of the tropical resident is a very important point. Men in business, especially Americans, are often intolerant of the country, its climate, and its people. They want a replica of what they are used to at home, and do not properly adapt themselves to a new country and a new climate. But the environment must be mastered, on penalty of death or disease. There are countless cases of people who should not go to the Tropics at all, just as some should not go to the Arctics — they should stay at home. Those who cannot take quinine should not go to malarious countries.

Dr. Deeks has spoken of diet. The diet natural to the countries in the Tropics is much more beneficial than the canned-food diet imported from the North. I think we have no conception of the mischief done by canned food in the Tropics. The natives have lived in these countries for many generations, and in their food and dietary habits they are much more rational than we are.

I want to mention one thing more, and that is the physical type of the natives. Sir Thomas Oliver and I have measured nearly 100 natives on this island. They have a very inferior breathing capacity as compared with other types. They simply do not know how to breathe. By inculcating proper deep-breathing habits, I think, we could eliminate much tuberculosis and other chest affections.

One word on the necessity of examining recorded facts. When I was on the Madeira-Mamore Railway I secured a record of all the deaths that had occurred from time of construction to date. It is

amazing what we can learn from past experience. Nothing is more regrettable than the neglect of such experience. I should have spoken of a paper by Dr. Eijkman, in the *British Medical Journal*, in which he refers to many of the points mentioned by Colonel Ashford. I recommend the article to you.

TROPICAL SPRUE IN PORTO RICO — A SYNTHESIS OF FIFTEEN YEARS' WORK OF INVESTIGATION AND 2,200 CASES.

Bailey K. Ashford, M.D.

The object of this paper is, first, to review the clinical conception of sprue; second, to briefly consider certain phases of its etiology.

Although the fact is not generally appreciated, the clinical recognition of sprue is about as indefinite as its etiology is supposed to be. Upon what clinical bases should we suspect or diagnose this disease?

The present conception of what should constitute sprue reminds one of the days when anything short of blatant "phthisis" with hemorrhage from the lungs was apt to have been diagnosed chronic bronchitis. To defer the diagnosis of sprue until the patient is entering upon the stage of cachexia makes the outcome dubious, if not in many instances quite hopeless, owing to permanent changes in digestive glands and the results of continued denutrition. It is the advanced, so-called "typical," picture of the older authors that is sought by the young practitioner in the Tropics today, and he is all too often apt to wait until he gets it.

As we review the literature, it will be found that a number of well-qualified observers have considered sprue a state or condition, although the majority have believed it a disease of unknown etiology, probably of microbic origin. Lowered cellular vitality from unhygienic living, and very especially from an ill-balanced diet, is certainly the usual stage from which Koch's bacillus acts its part, and there is reason to believe that the sequence, nutritional unbalance, digestive glandular incompetence, and a consequent acid-sweet, fermenting mass of undigested starches, sugars, and fats in the human intestine, affords the yeast-budding fungus, *Monilia psilosis*, a preferred medium for colonization. The writer believes that the symptom-complex resulting from the above-mentioned nutritional unbalance, enhanced as it may be by all of the varied factors found in tropical climates to

produce exhaustion-states, is the usual predecessor of sprue and is all too often confused therewith.

This symptom-complex is extremely frequent in Porto Rico and is popularly attributed to climate. The leading features in 227 cases of individuals suffering alone from this condition were: (1) disordered digestion, with acid dyspepsia and excess of intestinal gas, (2) constipation, with or without occasional loose movements of the bowels, (3) a steady diminution in the size of the liver, (4) a sallow complexion, (5) a lowered blood-pressure, (6) asthenia, and (7) a moderate loss of weight.

In 26% of these cases the tongue was sensitive to mild irritants, such as pickles or smoking tobacco; but there were rarely any lesions, and these, when they occurred, were limited to small aphthae of the buccal cavity, or fleeting erythema of the tip and edges.

Together with all of the above, there was an indefinable "nervousness" or nervous irritability, with psychic depression and a tendency to forget the little nearby details of life. There were vague pains in the body and palpitation of the heart, slight numbness and coldness of hands and feet; and in 24% of the cases, muscular cramps in legs, at times in hands, and, rarely, even in the muscles of the throat. The genetic function of males was frequently diminished, the menstrual function of females diversely disturbed. A common phenomenon was a faint brownish-gray pigmentation over malar prominences, forehead, cheeks just anterior to the ears, and, at times, symmetrically over the whole body. This may become so pronounced as to positively disfigure the features.

In none of these cases was *Monilia psilosis* found, and all serologic tests were negative.

Clinically, such cases are universal. They are more frequent in the hot countries, especially in individuals subjected to great mental strain, in the course of wasting diseases, after prolonged lactation, etc., but such a banal syndrome is familiar to physicians the world over. That cases of this kind in Porto Rico are largely due to an ill-balanced diet, is seen in that a correction of these dietary defects effaces the picture. But they do not warrant a clinical diagnosis of sprue, however they may suggest its possible oncoming.

This is the syndrome from which the peasant of the Porto Rican mountains suffers, although he rarely goes from it to sprue. It is the condition in which he is invaded by *Necator americanus*, and this condition had a large part in making *uncinariasis* so deadly in Porto Rico. (In the United States *uncinariasis* lowers efficiency for labor. In Porto Rico *uncinariasis* often kills with anemia, and was once responsible for 12,000 of the 36,000 annual deaths from all causes.) It is upon this background that tropical sprue most commonly develops. That it does not always require this background, will be seen later.

In sprue this picture is greatly enhanced. Not only are all of the components of this syndrome present, but most of them are greatly accentuated. The tongue becomes unequivocally sore, and may reach a condition in which a mere inspection will suffice for a diagnosis. Under such circumstances the saliva is apt to be increased in amount, and more acid in reaction. This raw, burning sensation, increasing in intensity, may reach the esophagus, may be felt in the epigastrium, and may even involve the rectum where a desquamation similar to that in the tongue may be verified. The writer has seen two of these chronic rectites terminate in fatal cancer. Indeed, a severe vaginitis may be set up from which cultures of *Monilia psilosis* may be readily secured.

With this desquamatory inflammation of the digestive tube may be associated a decided tendency to an increase in gaseous distension of the bowel, and large, white or grayish-yellow, frothy, sour-smelling, fermented stools make their appearance. These often occur in the early morning with relative immunity during the day, although this is rather the exception than the rule. These stools are apt to lack pancreatic ferments, and to contain an excess of fat and fatty acids. In one case a single evacuation from the bowel reached the enormous quantity of 1,300 grams and contained 50% of unabsorbed fat.

It is said that abdominal pain in sprue is rare, as well as nausea and vomiting. In 944 cases, 40% complained of occasional pain which was at times severe, 43% of nausea, and 25% of occasional vomiting. When this triad of symptoms co-exists with hematemesis and hyperchlorhydria, as in the writer's experience on several occasions, some

cases even going to operation, practitioners in tropical regions, not blessed with the refinements of diagnosis, may well suspect ulcer. And in this connection, let it be borne in mind that Askanazy is reporting from Germany gastric and duodenal ulcers whose dominant organism is *Monilia albicans*, believed by him responsible for the lesion.

Thus an inflammatory process, an "atrophic inflammation," has entered upon the scene to produce sprue, and with this in mind let us add two very important facts: (1) the *sallowness* of the patient suffering from the faulty nutrition syndrome has become *anemia;* and (2) the loss of weight and asthenia have become very marked, reaching the point where the weary victim of physiologic decay in the Tropics becomes a sick man and an object of solicitude. There is probably no disease in which emaciation is greater and more rapid than in sprue. The accumulation of permanent fat disappears and the muscular atrophy gives good evidence of itself in the universal weakness of these patients. At first, the anemia is secondary, and there is merely a relative lymphocytosis of the small-celled variety; but gradually the hemoglobin sinks, the color-index rises, the erythrocytes become deformed, anisocytosis becomes marked, large and small nucleated red-cells appear, and, finally, a close counterfeit of pernicious anemia is by no means unusual. Decidedly, the anemia of sprue is a point of importance in its diagnosis.

At this point it will be well to record a comparative chemical study of urine and blood in sprue and the syndrome resulting from nutritional unbalance in Porto Rico. It will be observed that at bottom it is the nutritional unbalance which is responsible for the picture. The results can be summed up by saying that both in sprue and in pure nutritional unbalance there is a tendency toward retention of non-protein nitrogen and chlorides in the blood, with figures a little exceeding the maximum normal, and a fall to or below the minimum normal of urea, uric acid, and chlorides in the urine. This suggests renal insufficiency in liberating the waste products from the blood. The only real difference between the two is seen in a more exaggerated tendency toward a mild catarrhal process affecting the renal pelvis and tubes, in sprue.

THE URINE IN SPRUE AND IN THE NUTRITIONAL UNBALANCE OF PORTO RICO COMPARED

Volume in 24 hours:

Average of 37 cases of sprue, 1,278 cc. In nutritional syndrome, 1,172 cc.

Specific Gravity:

Average of 148 cases of sprue, 1,016. In nutritional cases, 1,014.

Reaction:

Of 142 cases of sprue, 87% were acid. In 35 cases of nutritional unbalance, 85% acid.

Urea:

Average of 135 cases sprue, 17.4 g. per liter. In 35 cases of nutritional unbalance, 15.77 g.

Uric acid:

Average of 85 cases sprue, 0.45 g. per liter. In 27 cases of nutritional unbalance, 0.45 g.

Chlorides:

Average of 131 cases sprue, 8.45 g. per liter. In 34 cases of nutritional unbalance, 7.60 g.

Sulphates:

Average of 26 cases of sprue, 2. g. per liter. In 4 cases of nutritional unbalance, 1.69 g.

Phosphates:

Average of 105 cases of sprue, 1.84 g. per liter. In 30 cases of nutritional unbalance, 1.94 g.

Albumin:

Of 166 cases of sprue, 30% yielded albumin; 9% gave more than a trace.

Of 46 cases of nutritional unbalance, 15% yielded albumin, 2% more than a trace.

Sugar:

All but 5 of 135 cases of sprue were negative for sugar; in those positive, only one had any appreciable amount (1%).

All of 37 cases of nutritional unbalance were negative for sugar.

Indican:

Of 144 cases of sprue, 71% were normal; 19% showed a moderate increase, and 10% a great excess.

Of 37 cases of nutritional unbalance, 65% were normal; 20% showed a moderate increase, and 15% a great excess.

Urobilin:

Not found in 23 cases of sprue, nor in 3 cases of nutritional unbalance.

Bile pigment:

Of 143 cases of sprue, 86% were negative; only 5% had more than a trace.

Of 37 cases of nutritional unbalance, only one showed a trace.

Sediment:

Oxalate of calcium crystals were noted in 20% of 55 cases of sprue, and in 46% of 13 cases of nutritional unbalance.

Cells of the renal pelvis were found in 23% of 55 cases of sprue; in 7% of 13 cases of nutritional unbalance.

Pyocytes were noted in 63% of 55 cases of sprue; in 38% of 13 cases of nutritional unbalance.

Hyaline and granular casts were found in 21% of 55 cases of sprue; in 23% of 13 cases of nutritional unbalance.

THE BLOOD, CHEMICALLY, IN SPRUE AND IN NUTRITIONAL UNBALANCE

(Expressed in milligrams per 100 mils.)

Sugar:

In 48 cases of sprue, average of 101 mgms.; in nutritional unbalance an average of 90 mgms. in 18 cases. Note should be made, however, of the fact that when 6 cases with over 120 mgms. of sugar are removed from the sprue series, the average falls to 94.1 mgms. The 6 cases of sprue of over 120 mgms. gave an average of 133 mgms. These were all old-standing cases and may explain the reason why Recio, of Habana, is reporting high blood-sugars in 6 of his cases.

Chlorides:

In 33 cases of sprue, average 528 mgms.; in 12 cases of nutritional unbalance, average 515 mgms.

Urea:

In 47 cases of sprue, average 17.01 mgms.; in 12 cases of nutritional unbalance 16.58 mgms.

Uric acid:

In 48 cases of sprue, average 4 mgms.; in 12 cases of nutritional unbalance, average 3.71 mgms.

Creatinin:

In 48 cases of sprue, average, 2.29 mgms; in 12 cases of nutritional unbalance, average 1.96 mgms.

Non-protein nitrogen:

In 47 cases of sprue, average 39.7 mgms.; in 12 cases of nutritional unbalance, average 38.18 mgms.

NOTE: I am indebted to Dr. Rafael Del Valle Sarraga, Chief of Division of Chemistry, Insular Health Department, San Juan, Porto Rico, for the major part of this work on the chemistry of blood and urine in these two conditions.

The writer must be pardoned for rehearsing a well-known picture, but it is for the purpose of bringing out the diagnostic points of importance in this disease, namely:

1. A high-relief picture of the syndrome of dietetic unbalance, on which is engrafted an atrophic inflammation of the mucous membrane of the digestive tract.

2. Rapid emaciation, with resorption of permanent fat.

3. A light-colored, fermented, fetid, acid, fatty stool without blood, excess of mucus or tenesmus, and,

4. An ever-deepening anemia, with a marked tendency toward the pernicious type.

Of 1,435 cases of sprue, about two-thirds of them clinically complete in moderate or severe grade, 1,202, or 83.7%, were positive, mycologically or serologically, or both, for *Monilia psilosis*.

Of 698 cases clinically free from any suspicion of sprue there were but 1.2% of carriers, but as each case was cultured out but once, the writer believes that persistence would have disclosed more. It is doubtful, however, whether such positives would throw much more light on the subject, as one knows that *Monilia psilosis*, like all yeast-budding fungi, is merely a *voyageur*, not a colonizer, in a normal digestive canal. In a heavily infected country, it is only when more than 1 or 2 of a 100 points of contact on Sabouraud glucose agar in Petri dishes (Anderson's method) yield colonies, that we are authorized to aver colonization in the human bowel, that we can be reasonably sure of infection.

There remains a class of cases which seems to negative the

rôle of *Monilia psilosis* in sprue. These are the cases of *sprue cachexia*. In such, this organism is notoriously more difficult to place in evidence. Moreover, the serologic test is much more frequently negative. In reality, however, one should remember that here we are treating with the end-product of sprue, a sequela of sprue, if you will. The dominant note is atrophy of glandular organs connected with digestion. The bowel is thin from wasting of these elements. The tongue is bereft of papillae, — shining and smooth. Its thin, almost undeveloped, makeshift epithelial layer is fragile, and easily traumatized by the chemical effect of being bathed in an intensely acid saliva, which in 24 hours should show its result. As a matter of fact, sudden acidity of the saliva is apt to be followed by a raw tongue under such conditions, and yet no *Monilia* may be cultured therefrom. This sudden rawness of the organ has given rise to the expression, "a bout of sprue." No explanation seems necessary for a lienteric diarrhoea with a bowel whose function has been so badly crippled.

THE ETIOLOGY

Predisposing Factors

Age. — About ¾ of the patients were between 20 and 60 years of age, and of these ⅔ were between 20 and 40. Children, however, are much more frequently affected than has been previously supposed, 1/10 of the 619 cases of 1921 being under 10 years of age; 4 children were under 1 year.

Sex. — Of 1,452 cases (series 1920, 1921, and 1922), 59% were in females.

Race. — Of 211 cases (series of 1915–1917) there were 174 whites, 21 mulattoes, and no negroes. In 16 cases the race was not indicated. This ratio is about sustained in all subsequent series. Sprue is quite rare in the full-blooded negro, and plainly discriminates against the white race in the Tropics, particularly in persons whose stock has come more recently from the North.

Residence. — One of the most ridiculous statements in the literature is to the effect that only persons from northern climates acquire sprue in the Tropics, and then only after a long residence therein. It is certainly true that such people are much more prone to suffer from the disease and more

severely, and that the longer their residence, the higher the incidence among them, but an astounding number develop sprue after only a very short residence in endemic zones, even after a short first visit to the Tropics. The old belief in immunity of persons native to the soil would seem to rest on the unfamiliarity of the observer with the native languages, and the lack of opportunity too bserve their illnesses. What is worth while considering is the development of true sprue in persons, on return to their northern homes, who had previously resided a longer or shorter time in the Tropics, and who had enjoyed apparent health while there.

Endemicity. — The distribution of sprue in the Tropics is also of great importance, and is commonly misconceived by Northerners. Sprue is a distinctly urban disease in Porto Rico. During an expedition of the Institute of Tropical Medicine to the mountains of the interior, in 1913, of 10,140 chiefly rural patients found suffering from all diseases, but mainly from uncinariasis, only 11 cases of true sprue and 19 suspicious ones were found, while about half of the 2,200 cases which were collected throughout a period of 15 years, and which formed the basis of this thesis, were residents of San Juan, a city of only 70,000 inhabitants. Perusal of the foreign literature reveals that even within a country said to be heavily scourged, there are innumerable regions, including their towns, where this disease does not exist.

Social State and Habits. — Sprue is a disease of the well-to-do, of the intellectuals, of those who can choose their food. While it does not always pass by the poor man, it is by no means a poor man's disease. It is, above all, frequent among those whose life is a sedentary one, and those who have to work hard to keep up an appearance of affluence. It is a deadly enemy of missionaries, school teachers, and those who drift to the Tropics from northern latitudes, and who cannot "eat the native food," but gorge themselves on canned goods, bread, and sweets. Of 179 cases (in series 1915–1917) 16 were wealthy, 134 were able to select their ration, and 29 were poor.

Climate. — While sprue is really a tropical disease, it is not climate that makes it so, *per se*, as there are many tropical lands, such as Brazil and the Panama Canal Zone, as well as certain tropical regions surrounded by endemic zones, that

seem completely free from it. Indeed, there is no reason to suppose that sprue may not invade places in the southern districts of temperate climates, such as Korea, as do other tropical diseases.

Physiologic Insufficiency of the Digestive Glands. — Physiologic strain, such as rage or fear, overwork, intemperance in eating and drinking, too frequent pregnancies and too long continued lactation or even a normal menstrual period, may precede a bout of sprue. Not only the strain of life, but also long-continued illness from other causes, and even a weakly constitution in sallow, nervous, undersized individuals, are all too often the opening wedge to sprue. We must, however, keep in mind the fact that sprue does not necessarily require these factors; if often develops very suddenly in persons apparently healthy and robust.

As far as the relation of sprue to other diseases is concerned, the generalities above noted will suffice to explain any seeming relation between this and other diseases, but advantage is taken of the opportunity to emphatically deny the supposed obligatory relation between sprue and dysentery. Amebic dysentery practically does not exist where sprue is rampant in Porto Rico, and bacillary dysentery now must be very rare, as sincere effort has been made to culture out the causal organism in a large number of cases of intestinal flux, but without success.

The real and practical point in considering digestive glandular insufficiency as a predisposing factor in sprue can be concentrated in what we scientifically know of this condition as it affects digestion and digestive glands prior to the disease, a condition which in turn is exalted when sprue becomes established.

Nutritional Unbalance. — We have at last arrived at what seems to be the great underlying predisposing factor in most cases of sprue. In order to understand the precarious food status of Porto Rico, we must remember that it is an island of only 3,606 square miles, with a population of 1,300,000 inhabitants, or about 300 persons to the square mile. It is practically given over to the production of sugar, coffee, and tobacco, and can never hope to raise enough crops for its complete sustenance, or support cattle and dairy farms in anywhere near sufficient abundance. Its agricultural la-

borers are sustained mainly by polished rice, beans, codfish, and wild tubers, as well as plantains and other fruits. There is only a calculated 44,000-quart supply of milk available per day, or less than an ounce per individual. Fresh meat is scarce and rarely consumed by the people; eggs and poultry are usually sold in the towns; and succulent green vegetables and leaves are well-nigh rare. There is, therefore, a deficiency in the complete protein molecule, in mineral salts, especially calcium, and in A substances. This spells serious food deficiency, and its resulting symptom-complex is clearly recognized among the poor of the rural, particularly of the mountain districts. But it is precisely among such people that sprue does not exist, nor, for that matter, pellagra. It is among the urban population, and generally among those who can afford to choose their food, eat bread, and sweeten their intestinal canal, that we find sprue.

As a matter of fact, however, there are two factors which bring about in many families who live well, or fairly well, in towns and cities a somewhat more attenuated but similar state of affairs: (1) The Island does not produce enough garden truck to supply the demand in the towns; (2) By reason of this, and owing to the imposition for many years, and from economic reasons, of an ill-balanced ration, the special food *deficiency* of the Island has become a food *habit*, and people no longer crave meat and fresh garden truck of the sort craved in the North.

Here enters another factor of importance, *carbohydrate excess*. It would be impossible to enter into an elaborate scientific discussion of this phase of the question, but it has been more and more borne in upon the writer that partial exhaustion of the sources of diastase and lipase must be considered. A few observations in Porto Rico go to support the contention by many observers, notably by Brown of Johns Hopkins Hospital, that such diminution actually exists in sprue. Moreover, the fermentation of cereals and sugar of commerce in the bowel of a sprue patient and the reduced fat-absorption from the intestinal canal, are suggestive. This hypofunction must be enhanced by poor nutrition of the digestive glandular apparatus through the deficiencies in the ration in Porto Rico.

Most works on tropical medicine state that the first effect

of the Tropics on northern visitors is exhilaration, and that later digestion becomes labored with subsequent enervation. May this not be in part due to the well-known tendency of these freshly arrived Northerners to excess in carbohydrates, often loaded against their will with grease, because of their distaste for unfamiliar and mawkish vegetables and freshly killed, tough meat of a tropical market? An over-plus of heat- and energy-producing foods would be likely to produce exhilaration, until by excess they would exhaust the production of enzymes destined to digest them. Thus might be explained another injustice done the long-suffering Climate.

To the question, "Why do you prohibit sugar of commerce and starch of cereals, and permit fresh fruits heavy with fruit-sugar, and vegetables loaded with starch?" we can as yet only reply, "We do not know the reason, but the fact that the prohibited articles are not tolerated we do know." Perhaps the molecule of fruit-sugar and vegetable starch will be found to be as varied as the protein molecule has by recent work been shown to be. Perhaps the molecule of fruit-sugar and vegetable starch is smaller, its radicals more loosely united, and more vulnerable to much weaker dilution of enzymes.

Such matters are questions for the future, and only demonstrate the vastness of our field for research.

Communicability of Sprue. — That sprue may be communicable seems to be justified by:

1. Its tendency to spread in families, in communities, and regions.
2. Its development, in northern countries entirely free from it, in persons who had left endemic foci in apparent health.
3. Its recent appearance in some rural districts of Porto Rico where it was previously unknown.
4. Its unlooked-for and sudden appearance in persons native to endemic foci, whose habits and residence had been unchanged throughout a previously healthful life; and its still more sensational invasion of new arrivals to these Tropics healthy residents of the North.
5. The corroboration of all these data by specific instances

cited in the literature, particularly by medical officers of the French Navy, who report epidemics among the officers and crew of sick-transports carrying hundreds of victims of Cochin China diarrhea after leaving Saigon for France.

But the communicability of the causative agent of sprue is not the main question. It is the medium in which it is sown that is vital.

Monilia psilosis. — Time does not permit of a description of this organism, but a few comments will not be amiss. Castellani's remarkable study of the yeast-budding fungi brings out quite clearly a positive fact: that *Monilia albicans* is not a species, but a plurality of species. In fact, apart from the charge of multi-personality, this organism labors under the additional charge of an uncertain parentage. There is hardly a class, a family, an order, to which Science has assigned the pathogenic fungi that *Monilia albicans* has not claimed. Vuillemin induced it to form endospores and ascospores and upon this the genus *Endomyces* was erected for it. Bodin says that it is an *Oidium*, and recently Fineman confirms this. The writer has never seen *Monilia albicans* (*sensu stricto*) as defined by Castellani, acidifying milk and liquefying gelatin — although he perfectly realizes that this variety must exist — nor has he seen *Endomyces albicans* of Vuillemin. Elders sent us from Holland *Oidium albicans*, which was positively not *Monilia psilosis* and was so different as to make morphology alone a definite proof thereof.

Most studies of these yeast-budding fungi have been conducted with bacteriologic technique unfitted for the study of fungi, and totally inadequate to accurately differentiate them.

So far, apparently, the sources of sprue and thrush are remote, the one from the other, one in the Tropics, the other in temperate climates, and intense clinical and laboratory study of one is not complemented by a synchronous investigation of the other.

It is enough to say, by contrast, that if such a mongrel organism as *Oidium*, alias *Endomyces*, alias *Monilia albicans*, has been the universally accepted cause of infantile thrush since 1853 (a condition, by the way, which also requires a

denourished subject for its development) then we can with fairly good grace accept *Monilia psilosis* — a consistently described organism, with exceedingly slight and logical variations in culture — as a cause of a disease in which it is as consistently found in the presence of an unvarying clinical picture as is *Treponema pallidum* in syphilis. There is also the additional circumstance that *M. psilosis* is always recognized by the laboratory technicians of our Institute of Tropical Medicine, in Porto Rico, who never know whether the blood and feces upon which they are to render a report comes from a case of sprue or a control. It will also appeal to all that this organism has fulfilled Koch's postulates, and the production of a membrane on the tongue must be very rare as I have never seen it in any of my cases. Moreover it has been found in cases of sprue by Rogers and Patterson in Korea, by Dold in China, by Wood and many others in the southern part of the United States, by Recio and others in Cuba, and by Gonzales in Venezuela.

It looks as if it were *Monilia albicans*, and not *Monilia psilosis*, that needed investigation.

Virulent *Monilia psilosis* is pathogenic by inoculation for rabbits, guinea-pigs, and white rats, causing a fatal septicemia with concentration of the organism in the lungs and kidney. Passage through a series of animals greatly increases virulence, killing them in a few hours apparently by an endotoxin, as no soluble toxin has been found. Conversely, the repeated inoculation of *Monilia psilosis* of attentuated virulence produced immunity to the most virulent strains. By the addition of this organism to the normal food of monkeys, a fermentative diarrhoea, excessive production of intestinal gas, anemia, and marked emaciation were produced. By feeding 14 normal guinea-pigs with 7-day glucose-bouillon cultures of *Monilia psilosis* whose virulence had been augmented by passage, 10 died within about two weeks. The culture was simply poured over their usual diet of green leaves; 3 of these developed buccal excoriation and fermentative diarrhoea.

In addition to these experiments, it was found possible, by passage through laboratory animals, to reinvest *Monilia*, isolated from cases of clinical sprue, but which presented

deviations from the normal type in differential culture, with all of the cultural and morphological characteristics of the sprue organism.

I have not come here to deliver a lecture, nor to insist on my point of view in this vexed question of the etiology of sprue. I have come to learn, and to deposit as quietly and unostentatiously as possible my little bundle of observations amongst you, to add to those you have brought in the interests of tropical medicine. But I would not be frank if I did not again repeat what I have long since come to believe, that *Monilia psilosis* has a deal to do with tropical sprue. Perhaps, as Castellani and Chalmers have said, and others have repeated, yeast-budding fungi may account for only part of the picture, but I believe that this part is the part that authorizes us to give the disease a distinctive name and to consider it a clinical entity.

DISCUSSION

Dr. Aldo Castellani (*Opening the Discussion*). — We have seldom listened to a more interesting address. Colonel Ashford has given us the results of a very thorough investigation which has extended over 15 years. I am in complete agreement with Colonel Ashford on several points. As regards the geographical distribution, there is no doubt in my opinion that sprue, although much more frequently met with in the Tropics, is a cosmopolitan disease.

Sir James, Cantlie, I myself, and others have come across cases of true sprue in Europe and in England. Colonel Ashford has quoted cases from Korea, and cases also in various parts of northern China have been described. It is much more common in the south of China, especially in Hong Kong; it is common also in Singapore and in Ceylon, in the latter country being known as *Ceylon sore-mouth*. The disease principally attacks people of the educated classes, while it is comparatively rare in the lower classes. I must say, however, that in Ceylon I came across cases of sprue among all classes, even among the coolies. In the East it is not so common in children as apparently it is in Porto Rico.

As regards this point, it is necessary to differentiate from sprue a disease which clinically is very similar to it, and which is fairly often found in children, also in temperate zones. This is *Coeliac disease*, characterized by the patient's passing abundant stools of whitish-gray color. There is also great wasting, but no mouth symptoms. Dr. Ashford has given us a very good clinical picture of sprue, and I agree with him that the principal symptoms of the

disease are the following: (1) the stomatitis, (2) the gastro-intestinal dyspepsia with white frothy diarrhoea, and (3) wasting and anemia.

Etiology of the Malady. — This is a very difficult point. Personally I think that we do not yet know the causative agent of sprue.

At the present time, all we can say is that the *Monilia* plays probably a secondary role which may perhaps be the cause of some of the symptoms of sprue as, for instance, the frothiness of the stools.

Here I should like to state that in my experience there is a true *Blastomycosis* of the intestine. I have seen few cases, but the stools are not white, they are brownish, and at the autopsy you find blastomycetic ulcers in the intestine.

As regards treatment, I am in agreement with Colonel Ashford, that diet is the most important item. What diet shall we give a case of sprue? There are no fixed and dry rules. We are treating the patient and not the disease. Most patients do quite well on a milk diet, but about 20% of them cannot stand milk; then a meat diet in my experience is the best.

Drugs. — Any number of drugs have been recommended. I have tried recently calcium-lactate and parathyroid-extract. In a certain number of cases the result has been satisfactory, but not in all.

Occasionally large doses of bicarbonate of soda are useful. In certain cases I give an extract of strawberries. Vaccines I seldom use, but at times a streptococcus vaccine helps in clearing the mouth lesions, as noted by Sir Leonard Rogers. In conclusion, I should like to say again that in my experience the most important item of the treatment is diet.

Sir Leonard Rogers. — I have listened with great interest to Dr. Ashford's paper, on account of the enormous experience he has had, while he has covered the ground so fully that there is not much to say. I have been interested in this subject for a long time, and last October there was a discussion at the Royal Society of Medicine, in London, in which I took the view that the etiology of sprue is not yet fully understood, but that it begins in some failure of the digestive process, which may be due to faulty diet as has been suggested today. While in India I found about one-third of the cases begin with "hill diarrhoea" at elevations of 7,000 or more feet; this was clearly a physiological deficiency, as removal to a lower elevation at once stopped the symptoms. Any such digestive failure may become complicated by secondary infections, such as the monilia infection described by Colonel Ashford, but in

my Indian experience I found a secondary oral streptococcal infection always present in cases with sore-tongue, and also in other cases, as the most important factor. This led me to use vaccines made of oral streptococci, with good results, which have been confirmed by Dr. Nichols of Ceylon, who found the organisms to be streptococci viridans.

I treated 50 cases in Calcutta by this method, in many of whom relapses had occurred after apparent cures in England, and the best evidence of its value, which was very generally recognized in the London debate, is that of 20 cases treated in the Tropics and then followed up for at least a year after the completion of the treatment, no less than 18 remained well and at work in the Tropics. As soon as the attacks of sore-tongue cease to recur, the bowel conditions improve, and in this stage I find patients put on weight very rapidly, — such as at the rate of a pound a day for several weeks at a time, if vitamines, especially B, contained in tomatoes and marmite soup, made largely from yeast, are added to the diet. However, I got no marked effect until after the use of streptococci vaccines for 2 or 3 months, and I attribute the beneficial effects of strawberries and other fruits to their vitamine contents. I also give 20-grain doses of bismuth salicylate 3 times a day about 2 hours after food, and if necessary also Dovers powder in the morning to control the diarrhoea and fermentation until the effects of the vaccine can be obtained.

Dr. Seale Harris. — I have had very little experience with sprue. I have had occasional cases that seemed to me to present evidences of sprue, in which there was a question as to whether or not the cases were due to insufficiency of the pancreas. I am frank to say that in most of the cases in which I suspected sprue I was not positive of the diagnosis. It seems to me, however, that it is a disease in some respects similar to pellagra; that nutrition plays a very prominent part in the production of it: that by lowering the resistance it enables infection to occur.

In other words, it is an infection of the same sort, plus lowered resistance from an unbalanced diet. I have been impressed with two cases of diabetes — in which there were sore mouth and the severe diarrhoea with the large stools, frothy in character — which somewhat resembled sprue. In those cases I thought there was also the destruction of the glands of the pancreas involved in external secretion; and that with the absence of the enzymes of the pancreas, there follows intestinal disturbance, often diarrhoea.

Dr. J. W. W. Stephens. — Dr. Stephens said a good deal of emphasis has been placed on "dietetic unbalance." He then went on to speak as follows: —

I have no definite idea of exactly what is meant by this expression, but if there is any place where dietetic unbalance exists it must be on the West Coast of Africa (where I have lived on canned foods for months at a time) and yet, among the cases of sprue I have seen during the last 10 years, I can recall only one case (not completely typical) from West Africa.

I experience difficulty in the diagnosis of sprue. A patient with sore-tongue, with white frothy stools which microscopically show gas, and oil globules from which radiate sheaves of crystals, is a case of sprue. But a patient with no signs and only a vague history of sore-tongue, with only two or three movements daily — which are semi-solid, are hardly pale, in fact are bile stained, and which may microscopically show only some doubtful excess of fatty crystals — presents quite a different problem. Such cases require mature judgment in arriving at a diagnosis.

Stress is laid in the text books on the *indicanuria* as a sign of sprue; I took the trouble to find out that about 20% of normal, healthy people have indican in the urine, and that a healthy person may give as intense a reaction as a sprue case. "*Acid saliva*" is another "aid to diagnosis," but "acid saliva" is an exceedingly common normal phenomenon. Excess of fatty crystals in the stools is yet another aid, but here again patients with dysentery diarrhoea — also normal people — show the same sign, and so with *achlorhydria*. The kind of case I have mentioned above should be called sprue only after very careful consideration; many of them I believe are not sprue.

The diagnosis from pneumonias, pernicious anemia, and pancreatitis is also not always an easy matter. As regards symptoms, how often does Dr. Ashford observe tetany? Concerning treatment, I am in general agreement with what has been said, and all the cases I have treated in Liverpool have done remarkably well on a "regular" diet — a diet which starts with small quantities of meat at regular intervals, 4 to 5 times daily. The first result of this is that patients lose weight. In the 2nd week, the weight goes up; they make steady progress, and later recover. Castor oil in ½ drachm doses is useful in treating the distention, and the patient is extremely grateful for the ensuing comfort.

Dr. Aristides Agramonte. — I am very much interested in the question of sprue. I am afraid that I cannot add very much to the excellent paper presented, but, at the same time there are 2 or 3 points to which I want to call attention, having seen a few cases — I will not say how many, for fear you would compare them with Colonel Ashford's 2,000 cases.

The question of etiology, to my mind, is one that has not been

absolutely determined. I think that when all this evidence is sifted, we shall come to the conclusion that at the bottom of this process there is really an endocrine insufficiency, and that upon this condition of things (which we know depresses vitality through lowered resistance) become engrafted a series of infections which give us that complex syndrome of the disease. This is brought to my mind by the fact of its wide geographic distribution, and by the remarkable incidence of the disease, with greater prevalence in the Tropical Zone, where, as we know, the vitality of an individual is more or less depressed.

I must take exception to some of the remarks made by Dr. Stephens. As regards the diagnosis of sprue, I do not think it is more difficult than many other diseases which we come in contact with. In none of them do we make a diagnosis alone from the presence of glossitis or diarrhoea. When glossitis, diarrhoea, anemia, loss of weight and strength co-exist, by putting all these together I think that it is not very difficult to make a diagnosis of sprue. It is less difficult to skip or overlook cases of sprue than to diagnose them as such.

The example of pernicious anemia that Dr. Stephens brought out, is a case in print. Certainly in pernicious anemia we do not have diarrhoea as one of the symptoms, and very often no great loss of weight.

As to the treatment, which is what interests us most, I am convinced that, expressed in a general way, an anti-diabetic treatment is the thing. To this are added certain drugs to alleviate symptoms, and we get results in the majority of cases. There are certain cases which we find extraordinarily cachectic, in which we can do little or nothing, and the patient goes on to death. We should always insist on a balanced diet, adding a few drugs such as pancreatine, iron, etc.

One point that I think is of paramount importance, is rest. If I cannot put a man to bed I will not handle his case. I have in mind a patient who remained sick for about 6 months because he refused to go to bed. He had great interests in the United States and traveled back and forth on this account. He became really sick before he submitted to treatment, and after I had had him in bed for about 8 weeks the results were astounding. With hardly any treatment — first on an exclusive milk, then a meat-ball, diet, the man rapidly improved and finally regained his health.

Dr. W. E. Deeks. — Colonel Ashford's paper has been very interesting, in that he finds a large number of sprue cases in Porto Rico. In our experience, in other tropical countries typical sprue is rare. We meet with a considerable number of cases with clin-

ical symptoms similar to those described by Colonel Ashford as characteristic of sprue, but we do not see the frothy evacuations which are characteristic of that disease. We see many cases with red, irritated tongues, chronic pharyngitis, esophogitis, symptoms of gastric irritation, diarrhoea, proctitis in men, vaginitis in women, occasionally with dermatitis, nephritis, and at times, accompanying this symptomatology, symptoms of cerebral irritation.

We have called these cases pellagra believing them to be caused by an unbalanced diet in which excessive amounts of carbohydrates and insufficient amounts of green vegetables and fresh fruits are used. We have never looked for monilia infection in these cases, and it is quite possible that cases of sprue with frothy evacuations have the same predisposing factors as we find in pellagra, plus a super-added monilia infection which is responsible for the enormous frothy stools characteristic of sprue.

I have been frequently called to see cases of so-called sprue, but have found them almost invariably to be cases which yielded rapidly when a properly balanced diet was administered, supplemented usually by the administration of 15 drops of dilute nitric acid with essence of pepsin, in a tumbler of water before meals. It is quite possible that the good results reported in the treatment of sprue with diets confined to milk, meat and strawberries, and other agents, is the result of cutting out excessive carbohydrate diet, which I believe to be the underlying factor. In my experience, I have treated only one case of typical sprue, who contracted the disease in Porto Rico. This case yielded rapidly to the method of treatment I have just described; in fact, I had almost ceased to believe that sprue was an entity separate from pellagra, until I heard Colonel Ashford's interesting paper, in which he records the more or less constant presence of monilia in the stools.

It is particularly important for tropical residents to incorporate in their diets generous quantities of green vegetables and fresh fruits, and to limit the amount of their carbohydrates. This is particularly applicable to those who take little exercise or who follow sedentary occupations.

Dr. Foster M. Johns. — The question of the differential diagnosis between sprue and pernicious anemia has been raised. We are called on almost daily to differentiate such cases, and, apparently do so on the basis of the cardinal outstanding factor of achlorhydria in pernicious anemia, as contrasted with the evident carbohydrate dyscrasiae in sprue. Sprue gives quite a definite picture, in examination of the stools, with active fermentation of carbohydrates and the presence of yeasts in the early stages, and a marked fat-residual later. In pernicious anemia the first symp-

tom is the undigested meats found in the residue. The administration of hydrochloric acid will usually clear up the diagnosis, the diarrhoea of pernicious anemia clearing up rapidly.

Dr. Bailey K. Ashford (*Closing the Discussion of His Own Paper*). — I wish to thank my friends who have collaborated in this very vexed question. I would like to refer to some of the remarks made by Dr. Castellani, with regard to the rôle that *Monilia psilosis* could play in this disease, sprue. He made a comparison which I think could hardly hold good in this disease. Referring to the relation monilia bears to sprue, he likens it to the secondary infection by staphylococcus which causes the more annoying symptoms of scabies. The real point is, *Monilia psilosis* is a primary, not a secondary, infection and abounds even when the disease sprue commences to make itself manifest clinically; if it is allowed to go on colonizing in the bowels, the complete disease will be produced. It is in the later phases of the disease, when cachexia is added to the picture, that *Monilia psilosis* seems to become scarcer.

With regard to the pathologic anatomy of sprue and the lesions produced in the bowel, this phase of the question is obscured by an insufficient number of autopsies. It is a fact that the most exhaustive work done in what was probably sprue, was reported by Kelsh and Kiener, in about 1880, in some 250 autopsies of cases of Cochin-China diarrhoea. They wrote a very extensive pathological history of those cases, and the ulcers they described were in the small intestine, and often superficial and small.

With regard to Sir Leonard Rogers' remarks concerning "hill diarrhoea," naturally this possibility has come into my mind several times, but not having seen "hill diarrhoea" I was afraid to draw the conclusion concerning what I imagined was a deficiency syndrome.

With regard to the therapeutic use of yeast, if it were possible to give this yeast pure, it might be helpful. I gave a commercial yeast manufactured in the United States, and the contamination was so bad I could not continue its use, — whether from infection in the Tropics or in transit, I cannot say. It upset some of my patients badly.

I wish to state that relapses after the use of *Monilia* vaccines seem not to be prevented. My impression is that there are many relapses after the use of vaccines.

With regard to Dr. Harris' remarks, I agree with him that malnutrition plays a great part in sprue and pellagra. From that background proceeds sprue in one direction with a distinct clinical picture, and in another pellagra.

With regard to diabetes, it is very interesting that Dr. Recio,

of Havana, considers high blood-sugar as peculiar to some of his cases of sprue. In all of 6 cases the blood-sugar was high. In 144 cases I had 6 which had an average of 133 mg. of sugar in the blood.

With regard to Dr. Stephens' estimate of sprue, I am very glad to see that he was not inclined to give too much emphasis to dietetic unbalance, and that in the West Coast of Africa we have another portion of the Tropics in which, as you can see, sprue seems not to exist. He has thrown cold water on his own diagnosis of sprue: there was no sore tongue.

With regard to indican, it is not so often high in sprue; in 71% of 144 cases it was normal.

Regarding tetany, I believe that at some time in the course of sprue we have it in 25% of the cases. I did not call it tetany when I spoke of cramps in legs, arms, and throat, but that is what I think it was.

With regard to pernicious anemia, it is very interesting that Dr. E. J. Wood, of North Carolina, has had 15 cases of pernicious anemia with a foregoing history that seemed like that of sprue. In some, he writes me, he was unable to find *Monilia psilosis* in the stools, but did culture it from under the gums.

With regard to the diagnosis, there are several features unmentioned by Dr. Johns. The fats are not absorbed well in sprue, and there is an abnormally high percentage in the stools. In pernicious anemia you do not ordinarily have loss of flesh; in sprue it is very marked.

I do not believe that Dr. Stephens would have any difficulty in diagnosing sprue clinically in a place where it was very frequent. They die of it in large numbers in Porto Rico. The Spanish called it *intestinal phthisis,* and were much afraid of it.

Dr. Agramonte mentioned endocrine insufficiency. I have been really diffident in mentioning this, on account of the present chaotic state of endocrinology, but I agree with him that it exists in sprue. There is one thing certain, that there *seems* to be a decided and consistent adrenal insufficiency in sprue. I agree with him in regard to the necessity for rest in treatment; but a great many of our men are unable to rest, on account of their business.

With regard to Dr. Deeks' remarks, I see that he is in agreement with the dietetic syndrome, which I prefer to call a background for sprue. But this background does not always accompany sprue. We have a number of patients who come down to Porto Rico from New York, live at a hotel, and then go back North and there have sprue. The great point to determine in Dr. Deeks' cases with only the dietetic syndrome is, Do they die of this thing he describes?

In Porto Rico they *do* die of sprue in large numbers, in spite of everything.

The Treatment of Sprue. — In 95% the cases have a liberal diet from which is eliminated sugar of commerce and the cereals. The other 5% must be fed on milk alone, or on Cantlie's meat diet. When a person is not doing well on a liberal diet of vegetables, fruits, and animal proteins, we give him castor oil, and put him on ⅓ lb. of chopped meat every 3 hours on 6 occasions daily, always preceding each feeding with a cup of hot tea. I use such eupeptics as may be necessary, pancreatin and diastase, 5 grains of each after each meal, etc.

Hydrochloric acid is at times given when there is hypochlorhydria. I tried in 1920 or 1921, on purely theoretical grounds, parathyroid extract, $\frac{1}{10}$ of a grain, combined with 10 grains calcium lactate. I could not see any appreciable betterment from this combination, in a large proportion of my cases, although Dr. Scott had very good results with this treatment. Perhaps my parathyroid glandular extract was not fresh. There is calcium deficiency in at least the cachexia of sprue, and the administration of calcium is not only rational but seems to be a favorite method of treatment in the Far East.

One has to admit that sprue is a *moniliasis*, to use *Monilia* vaccines.

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THE FOOD FACTOR IN PELLAGRA

SEALE HARRIS, M.D.

Since Casal described pellagra in Northern Spain in 1735, food has been under suspicion as being the most important factor in the etiology of the disease; and since the area of distribution of pellagra in Europe corresponded with the countries in which maize is the most important source of food supply, corn products have been thought by many observers to be the source of the disease.

Prior to the first described epidemic of pellagra in the United States, at Mount Vernon, Alabama, in 1906, most of the literature on that subject was contributed by Italians; and the view of Lambroso that some unknown factor in corn is the cause of the disease, was accepted as explaining the probable cause by many Southern physicians. Ceni's theory that pellagra is due to a toxin elaborated by an aspergillun which grows in damp corn was also considered. Sambon's belief that pellagra is an infectious disease transmitted by the bite of the simulium reptans was discredited because, in some localities in the South, that variety of fly does not exist. Alessandrini, another Italian, was convinced that a deficiency of silicon in the diet is the etiological factor in pellagra, but this theory did not seem to account for the prevalence of the disease in the South.

After the publication of the Alabama cases, with a description of the symptoms, pellagra was found to exist in the rural districts of all the Southern States; and a few sporadic cases, and one or two small outbreaks, or epidemics, were reported in Ohio and Illinois. A number of observers began making investigations, and soon the literature on pellagra in the United States rivaled that of the Italians, and there were many divergent opinions on its etiology, on the part of American physicians.

American Theories on the Etiology of Pellagra. — The first thorough study on the etiology of pellagra in the United States was made by the McFadden Pellagra Commission[1]

[1] SILER, GARRISON and MACNEAL. "Studies on Pellagra." *Archives of Internal Medicine*, 1914, XIV, 293.

of which two very competent men, Siler and MacNeal, were the leading investigators. They made careful studies of the food conditions and hygienic environment of pellagrins in the cotton mill districts of South Carolina. They were convinced that pellagra is an infection of some kind, suggesting that the ordinary stable fly (*Stomoxys Calcitrans*) found everywhere in the South, might carry the disease from human excrement to unprotected food. They pointed out that pellagra was never found in cities and towns having a good sewerage system. The late Isadore Dyer, formerly Dean of Tulane Medical School, concurred in that opinion; and the many cases that I have had to treat, all came from the country districts, or from the suburbs of cities which had open privies.

Goldberger[1] believing that pellagra is due solely to an unbalanced diet, produced the disease experimentally by feeding a group of selected prisoners on a diet consisting largely of corn-meal, grits, potatoes, fat meat, syrup and sugar, a diet similar to that of many poor whites and blacks in the rural districts of the South. Goldberger's experiments — added to the fact that many clinicians had found that by feeding pellagrins on a diet rich in milk, eggs, meats and vegetables the disease was arrested or cured — caused the acceptance by many that an unbalanced diet is the only etiological factor in pellagra.

My opinion on the subject has not changed since I had the privilege of examining the first cases at Mount Vernon, Alabama, in 1906, *i.e.*, that nutrition is an important factor both in the etiology and the treatment of the disease, and that bodily resistance bears much the same relation to pellagra that it does to tuberculosis, though the seasonal outbreaks of pellagra pointed to a different type of infection.[2] I therefore feed my pellagra patients on much the same diet as is given the tuberculous patient; and with results equally as good as those obtained by the Italians, who for half a

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[1] GOLDBERGER. "The Cause and Prevention of Pellagra," *U. S. P. H. S. Report* No. 218, September 11, 1914; "Experimental Pellagra in the Human Subject," *U. S. P. H. S. Report*, No. 311, November, 12, 1915.

[2] HARRIS, SEALE. "The Digestive Symptoms and Diet in Pellagra." *Texas, State Journ. of Medicine*, August, 1915.

century had fed their pellagrins on a full diet, with a reported death-rate of less than 5%.

Lussana and Frua[1] in 1856 claimed to have reduced the mortality from 24.5 to 4.5% by improving the diet of 8,000 pellagrins. The increase in food given to pellagra patients shortened the time of convalescence in their cases by from 20 to 70%.

The Effects of Lowered Resistance. — One of the early publications on pellagra in the United States, and one that really blazed the way to what I believe will eventually prove to be the most important predisposing factor in the etiology of pellagra, was by Deeks[2] who pointed out that the pellagrins which he had seen in the Canal Zone were in a lowered state of resistance from a diet rich in carbohydrates, particularly sugars. Deeks also believed that this unbalanced diet was responsible for many cases of tonsillitis, arthritis and other infections, in that a person in an imperfect state of nutrition is more susceptible to all infections.

Funk[3] was probably the first (in 1910) to announce that pellagra probably is due to a deficiency in vitamins, and he classed it as similar to beri beri.

McCollum[4] in his early investigations, was inclined to believe that pellagra is solely a deficiency disease, but later announced the opinion that an improper diet is a predisposing factor and that some sort of an infection is the exciting cause. The following is an exact quotation from McCollum's book: —

> McCollum, Simonds and Parsons were inclined to interpret their results as supporting the view that pellagra is an infectious disease, and that the role of diet in its etiology involves only increased susceptibility to infection, due to lowered resistance caused by faulty diet persisted in during the winter months by many people in the South.

[1] LUSSANA and FRUA. "Sufla Pellagra," Milan, 1856.

[2] DEEKS. "The Carbohydrates as Etiological Factors in Stomach Disorders," *New York Medical Journal*, June 25 and July 2, 1904. "The Etiology and Treatment of Pellagra," *Southern Medical Journal*, November, 1922.

[3] FUNK, Reference to work of, in McCollum's "Newer Knowledge of Nutrition," 1922, p. 18.

[4] MCCOLLUM. "The Newer Knowledge of Nutrition," *MacMillan*, 1922, p. 282.

Voegtlin[1] of the United States Public Health Service, working on the theory that pellagra is due to a deficiency in vitamins and certain amino-acids and also to the presence of toxins, made a valuable contribution to the study of pellagra; though in the opinion of McCollum, Voegtlin did not prove that the food factor is the only cause of the disease.

McCarrison[2] has given us what, in my opinion, constitutes the key to the etiology of pellagra and to many other diseases either known, or believed by many, to be due to infections. It is but just to say, however, that McCarrison's investigations seem to prove what Deeks has believed for a quarter of a century: — that lowered resistance from an unbalanced diet predisposes to many infections. McCarrison, a British Army Surgeon, stationed in a remote region of the Himalayas, was impressed by the rugged health and longevity of the inhabitants whom he treated, though they lived under most unsanitary conditions. He said: — "During the period of my association with these peoples I never saw a case of asthenic dyspepsia, of gastric or duodenal ulcer, or appendicitis, of mucous colitis, or of cancer, though my operating list averaged 400 major operations a year." In his investigations as to the cause of this remarkable freedom from abdominal diseases among the primitive Himalayans, he was convinced that the use of "natural foods — milk, eggs, grains, fruits and leafy vegetables" — protected them against infections.

McCarrison's Experiments. — McCarrison's classical experiments seem to prove that foods of low vitamin value and deficient in certain mineral substances, if used over long periods of time, predispose to infections of the gastro-intestinal tract. He also called attention to the effect of an improper diet on the endocrine function. He placed 36 health-monkeys in separate cages in the same room — 12 were fed on natural foods, and 24 on foods excessive in carbohydrate content, deficient in vitamins, and lacking in various mineral substances. Of the first group all remained healthy and free from intestinal disease, while a majority of those fed on un-

[1] VOEGTLIN, C. "Studies in Pellagra," etc. *U. S. P. H. S. Reports*, 1920.

[2] MCCARRISON, R. "Faulty Food in Relation to Gastro-Intestinal Disorder." *Journ. Am. Med. Ass.*, 1922, Vol. 78, No. 1, p. 1.

balanced and deficient diets developed diarrhoea and actual dysentery.

McCarrison is of the opinion that Vitamin C serves to protect the gastro-intestinal tract from infections; and that the deleterious effects of a deficiency of this vitamin is enhanced when the food is improperly balanced, particularly when associated with an excess of carbohydrates, or fats, or both in the food. Again, quoting from McCarrison: "Impairment of the protective resources of the gastro-intestinal mucosa against infecting agents may be due to hemorrhagic infiltration, to atrophy of the lymphoid cells, and to imperfect production of gastro-intestinal juices. This impairment not only results in infections of the mucous membrane itself, but also permits of the passage into the blood stream of micro-organisms from the bowels."

McCarrison showed, by illustrations of sections of various parts of the intestines, that all these changes occur in animals that have been fed on diets poor in vitamins and with an excess of carbohydrates. He claims that "diarrhoea, dysentery, dyspepsia and gastric dilatation, gastric and duodenal ulcer, colitis and failure of colonic function can be produced experimentally by means of feeding animals on faulty food." He does not claim that the faulty diet is the only cause of these gastro-intestinal conditions, but insists that pathogenic organisms are contributing factors. As proof that a faulty diet lowers resistance to infections, McCarrison fed healthy monkeys on *entamoeba histolytica* and failed to infect any of them; while those fed on a deficient diet became readily infected, when given the *entamoeba histolytica* organisms.

The Application of McCarrison's work to Pellagra. — The diet, fed by McCarrison to monkeys, that resulted in various lesions in which pathogenic micro-organisms were a factor, is not unlike that of many of the inhabitants of the rural districts of the South and elsewhere. It is much the same diet, deficient in Vitamin C and excessive in carbohydrates and fats, that Goldberger used in producing experimental pellagra in human beings; but McCarrison insists that faulty food lowers resistance to infections of the gastro-intestinal tract, while Goldberger maintains that an unbalanced diet is the sole cause of pellagra.

There are the defects in Goldberger's experiments that

they were carried out in a region in which pellagra exists, and during the summer months when the disease is most prevalent. If Goldberger's experiments had been repeated successfully in Maine or North Dakota, there are many physicians in the South who would accept his views, but who now believe that pellagra is due to an infection. Few physicians in the South who have had clinical experience with pellagra, agree with Goldberger that the unbalanced diet is the sole cause of the disease, or that it is even a factor in every case, because many us have had cases in wealthy families whose history showed that they had lived on a well-balanced diet. Personally, I should like to believe that faulty food is the only factor, but it seems to me that the evidence points to some form of infection as the exciting cause of pellagra.

The geographic distribution of pellagra, the seasonal occurrence of the symptoms, and the fact that it is a rural disease in localities in which soil-pollution is practiced, all point to an infection. It is also significant that the very marked reduction in the morbidity and mortality from pellagra in the Southern portion of the United States, has been coincident with improvements in sanitary conditions, particularly with reference to soil-pollution; and there has been a corresponding reduction in the prevalence of uncinariasis, amebiasis and typhoid fever. I have not been able to observe any marked improvement in the diet, in the last few years, among the rural inhabitants of the South since pellagra has decreased surprisingly. The South is not the only region of the United States in which there are people who live on an unbalanced diet. Nutritional studies of school children in Massachusetts show that about 20% of them are under-nourished, about the same proportion as found among the school-children of Tennessee. A high-carbohydrate, high-fat diet is not uncommon in the cities all over the country, in which meat is the most expensive article of diet, yet pellagra does not exist in them. There must be added an infection agent to produce pellagra.

The Unbalanced and Deficient Diet of Europeans.[1] — If

[1] HARRIS, SEALE. "Food Conditions in Europe with Remarks on the Etiology of Pellagra," *New Orleans Medical and Surgical Journal*, February, 1920, Vol. 72 No. 8.

faulty food were the only factor in the production of pellagra, it would seem that the countries of Europe that suffered so much from a lack of meat, eggs and milk during and after the World War, would have been scourged with pellagra; yet the disease did not exist in some countries that suffered most from lack of food, and there was an actual reduction of the disease in Italy at a time when food conditions were most serious.

After the signing of the Armistice I made some investigations regarding food conditions and nutritional diseases in France, Belgium, Germany, Austro-Hungary and Italy; and, since I am particularly interested in the study of pellagra, made special inquiries regarding the occurrence of that disease. There was an actual shortage of food in France, though the French suffered less in that respect than the inhabitants of the other countries mentioned. I was stationed for 10 months in Paris and visited the War Zones and many localities in Central and Northern France, and there can be no question but that for 2 or 3 years the whole French population was under-nourished, particularly the poor, and as a result the general death rate, especially among the children, increased considerably. Tuberculosis was said to have increased enormously among the civil population, who were not so well supplied with food as the soldiers. Scurvy, particularly the infantile variety, which was said to have been scarce in France before the War, became quite prevalent. Likewise epidemics of Vincent's Angina, dysentery of the bacillary type, and the infections of childhood, prevailed as never before; but I could find no French physician who had seen a case of pellagra in central or northern France. It may have been present in southern France, a region that I did not visit. The French had almost no milk, butter or eggs, rich in Vitamin A, which protects against respiratory infections — hence the increase of those infections in France during the War. Apparently the French had plenty of proteins derived from meat, though all the fat had been removed. They had very little sugar and were rationed with bread. Their carbohydrates came largely from potatoes, beets, and wine, but they seemed to have had sufficient green vegetables and fruit. Therefore the French had a low-fat, low-carbohydrate and relatively high-protein diet. It is

but fair to say that the advocates of the unbalanced-diet theory as the sole cause of pellagra, would not expect the disease to develop on the French rations.

Food conditions in Belgium differed from those in France, in that there seemed to be more bread, furnished by the American Food Commission, but there was a shortage of meat, milk, eggs, and butter. I could find no pellagra in Belgium, though its inhabitants no doubt suffered much from an unbalanced diet.

No Pellagra in Germany in Spite of Their Unbalanced, Deficient Diet. — My investigations in Germany convinced me that the Germans suffered severely from lack of food the last two years of the War — the civil population more than the soldiers, though the German armies, even at the front, were on short rations. The rations for the civil population in Germany for the week ending February 1, 1919, were as follows: —

Bread 2,000 grammes, barley 100 grammes, potato-flour 100 grammes, potatoes 2½ kilograms, beet sugar 60 grammes, meat 150 grammes, margarin 35 grammes.

To this were added such vegetables as could be obtained, principally the sugar-beet and a coarse tuber the name of which I have forgotten. Fruits were rare. The Germans, therefore were living on a high-carbohydrate, low-fat, low-protein diet with a marked deficiency of Vitamins A and C. If an unbalanced diet alone would cause pellagra, the Germans would have had it by the hundreds of thousands; but I could find no physicians in Germany who had seen anything resembling pellagra. Tuberculosis, the infections of childhood, and other diseases due to the infections that existed in Germany, had increased enormously and they had many outbreaks of diarrhoeas; but there was no pellagra. It seems to me that this can be explained only by the probable fact that the infective agent necessary to produce pellagra did not exist in Germany.

A German dermatologist at Aachen said that there had been a very great increase in skin disease during the War, particularly those due to traphic disturbances, but that he had seen no lesions resembling the skin manifestations of pellagra. He attributed the increase in skin lesions among

the Germans partly to the lack of soap, a lack which made it impossible for them to keep clean.

Food conditions in Austro-Hungary were much the same as in Germany. I visited the provinces of Trent, Trieste and Croatia and there was a great shortage of meat and fats there, though they had more fruits than the Germans. There were said to be occasional cases of pellagra in the country districts near Trieste (none in the city), though those whom I interviewed told me there was less than before the War.

The Reduction of Pellagra in Italy.— In the United States we have been of the opinion that Italy was a hot-bed of pellagra, and I was surprised to find that it is now a comparatively rare disease in that country. Rome was the first place that I visited, and I expected to find many cases in their very excellent hospitals, but was told that there were no cases in Rome and one of the leading Italian physicians there told me that he had never seen a case of pellagra. I went to the office of the Surgeon-General of the Italian Army, hoping to get some statistics on pellagra among the soldiers, but was informed that only a few cases had been reported among the 5 or 6 millions of soldiers that had been drafted in Italy. The only thing by way of statistics that could be obtained on pellagra in the Italian Army, was the statement that in 1918 in the last draft of about 1,000,000 men there had been only 34 rejections on account of pellagra. I visited the Vital Statistics Division of the Italian Public-Health Service, and was informed by the Director that there had been an enormous decrease in pellagra in Italy in the last 20 years, but that he had no data to prove it.

Physicians in Rome said that there was no pellagra there but that it prevailed in Northern Italy. I was informed at the hospitals in Padua — in Northern Italy — where the Field Headquarters of the Italian Army were located, that there was no pellagra in that locality. At the American Hospital at Vicenza, in Northern Italy, in which many thousand Italian soldiers were treated, the medical officers, most of whom were from New Orleans and therefore familiar with pellagra, said they had seen no Italian with symptoms resembling those of pellagra, and that in so far as they were

able to learn there was no pellagra in that part of Italy. Diet could surely have nothing to do with the decrease in pellagra in Italy, since there was a very serious shortage of food, with much discontent among the civil population as well as among the soldiers, because of it. Apparently almost the whole Italian population was living on a high-carbohydrate, low-protein, low-fat diet, though on account of their fresh fruits they apparently did not suffer from a lack of the antiscorbutic vitamin, and since meat, milk or eggs, and wheat products were very scarce in Italy, the Italian diet was deficient in Vitamins A and B. The Italian diet consisted largely of corn-meal (*polenta*), rice (*yisotti*), potatoes, beet-sugar, vegetables and fruits, a diet that — according to the unbalanced-diet theory — would produce pellagra, and if there were no infectious factor, there should have been a marked increase in pellagra in Italy during the last years of the War, when as a matter of fact, there was a decrease of the disease. I found no Italian physician who would attempt to explain the cause of the decrease of pellagra in Italy, though all of those whom I met asserted it to be a fact.

Pellagra Probably Due to Infection. — I realize that the epidemiological investigation of a disease is not the best way to study its etiology, but it is surely suggestive that among the millions in Europe who were under-nourished, and living on much the same diet used to produce the disease experimentally in Mississippi, there were no cases of pellagra. Indeed, it appears that Goldberger's experiments were repeated by millions of Europeans who were forced to live on an unbalanced diet for years, and did not develop pellagra. This seems to me good evidence that the food factor is not the only element in the production of pellagra.

In studying Goldberger's experiments in Mississippi, it seems entirely possible that his patients may have been infected with some organism, whatever it may be, causing pellagra, at a time when in a condition of lowered resistance from having subsisted upon an unbalanced diet for several months.

The fact that various attempts have been made to infect human beings and animals with pellagra, without success, does not mean that some micro-organism is not responsible

for the disease. Goldberger[1] and Francis[2] of the United States Public-Health Service did some good work along that line, but they were dealing with healthy human beings and healthy animals. It has been found very difficult to transmit artificially diseases known to be infectious. It may be that in pellagra — as McCarrison found in his efforts to infect monkeys with dysentery — the properly nourished animal can resist the infection, but after a few weeks or months on an unbalanced diet the intestinal tract may lose its power to resist invasion from organisms in the intestinal contents. Since there are many who believe that pellagra is due to an infection, it would surely seem worth-while for research workers to continue their efforts to find the cause of the disease.

CONCLUSIONS

1. The unbalanced diet does not seem to be the only factor in the etiology of pellagra.

2. The food factor — *i.e.*, a diet low in Vitamin C, and unbalanced with an excess of carbohydrates — in lowering resistance, is an important predisposing cause of pellagra.

3. A full diet, rich in vitamins, particularly B and C with a low carbohydrate content, eliminating cane-sugar entirely, is essential in the treatment of pellagra.

4. The cause of pellagra has not been discovered. It probably is due to an infection of some kind, and further researches in the etiology of pellagra are suggested, taking into consideration that animals or human beings in a lowered state of resistance may be susceptible to infection, while the tissues of the well-nourished individual possess greater immunity to invasion from various pathogenic micro-organisms.

DISCUSSION

Dr. C. C. Bass (Opening the Discussion). — Pellagra is another one of those diseases which can be diagnosed only after they have developed to a certain advanced stage, and then perhaps only at favorable times. There is no reasonable doubt but that a great

[1] GOLDBERGER, J. "Experimental Attempts at Transmission of Pellagra to the Human Subject," *U. S. Public Health Reports*, Nov. 17, 1916, xxxi, 3159.

[2] FRANCIS. "Attempts to Transmit Pellagra to Monkeys," *U. S. Public Health Service Reports.*

deal of pellagra goes undiagnosed. During the time when pellagra was more prevalent in the United States than it is now, 10 or 12 years ago, I had occasion to study or observe the disease in a great many people.

One experience that impressed me very much was frequent discovery of evidence of the disease in members of the family, or close associates, of cases who at first stated that no other members of the family had the disease. If we followed up the other members of the family carefully, we often discovered evidence that they had the disease at the time, or had had it previously. In other words, we frequently got a history of similar conditions existing previously, perhaps a year before, but no evidence of the disease could be found at the time. A great deal of pellagra goes undiagnosed. We diagnose pellagra on the basis of certain characteristic skin lesions which are present during a comparatively short part of the year. At all other times they are absent. The attacks, with the definite clinical symptoms, may recur from time to time at long intervals. Therefore, the period of time during which the disease can be diagnosed is often extremely short.

With regard to the food factor as a cause of pellagra, I have not the slightest thought that we know the cause of pellagra, neither do I know of any evidence that food or a faulty diet have anything more to do with the cause of pellagra than they have with the cause of any other infectious disease. I should not be surprised to know that faulty diet may contribute to some extent to the development of this as well as other infectious diseases, but I greatly doubt whether diet has anything more to do with it.

I recall my enthusiastic efforts to confirm Lombroso's theory during this early period when we had hundreds of cases to observe. By getting the histories carefully, I was able to determine that corn had entered into the diet, usually spoiled corn or corn meal. As we went on with our investigation, we became more and more enthusiastic about it, and were quite convinced that we were on the right track. A case came in which originated in New Orleans. We could trace no corn in the woman's diet but learned that she was a drunkard. We followed up the clue and found that she drank *corn* whisky. This is just an example of how it is possible to find evidence in support of one's theory, if he follows it hard enough.

Opposed to diet as a factor in the production of the disease, is the fact that experimental pellagra in monkeys occurs in well-fed and well-nourished animals. That was first shown by the work of Dr. W. H. Harris, of New Orleans, some years ago. Although neither Harris nor the others who have tried have been able to repeat his results, I was convinced, and still am, that pellagra is an

infectious disease, transmissible from an infected individual to a susceptible one.

In conclusion, I wish to point out the fact that the low mortality of pellagra has misled a great many into believing that their particular treatment, including diet, has had favorable influence on the course of the disease. As a matter of fact, most of the pellagra cases get well anyway; very few die, as compared with the large number who have the disease. Whenever a patient is transferred from his ordinary conditions of living, to a hospital, his condition usually improves promptly and this improvement is often attributed to the treatment given, whatever it may consist of. As a matter of fact, they usually do get well, irrespective of the kind of treatment they receive. Therefore, I believe that the fact that patients improve on diet, or from any other specific treatment, is not sufficient evidence that the disease is caused by improper food.

Col. Bailey K. Ashford. — I was very much interested in Dr. Harris's paper, and both he and the last speaker have, I think, shown that the Thompson-McFadden Commission did not live in vain. Their work was not to find any particular causative agent, but they came to a very reasonable conclusion. No mention was made of the work of Jobling, in New York, who is working on certain fungi and their photodynamic effects in pellagra. He cannot continue the work, because he cannot get the cases. You will note that the first case of pellagra was found in Porto Rico, in 1904. An account of it is published in the 1904 report of the Porto Rican Commission. On an island opposite Porto Rico, St. Thomas, Dr. Christiansen, a Dane, a graduate of the London School of Tropical Medicine, had a very large group of cases of pellagra there. I think that he felt that diet did improve the condition of his cases.

Major Henry J. Nichols. — I have noted that most of the previous speakers who have spoken of the etiology of pellagra have reported themselves as being on the infectious side of the question; I wish to go on record as being on the other side.

It just happens that I was associated with Colonel Siler, who headed this commission, and it shows how different people can arrive at different conclusions in working on the same material. We investigated an epidemic in an insane asylum in Illinois, and I came to the conclusion that it was a food-deficiency disease, while he came to the conclusion that it was due to infection.

Reference has been made to the existence of pellagra among well-to-do people who are able to choose their own foods. We had one case of pellagra in the army, an officer. When it was reported, everyone said that this was an instance of pellagra where you could rule out the food factor. This officer was sent to the Walter

Reed Hospital. I personally went carefully into the history of the case with the patient's sister, and found that he had always been a crank on diet, had never eaten meat, and always carried crackers around in his pockets. Instead of throwing out the food factor in this case, it seemed to me that we might regard it as a striking example of food deficiency.

The only reason I wish to speak on this subject is that it seems to me the sanitarian who today is dealing with pellagra, and who disregards or fails to use the food theory, on the ground that it is probably an infectious disease, is taking some liberties with the situation. It seems to me that we had the same situation with regard to beriberi some years ago — whether it was an infectious disease or not. As soon as we changed the diet of our troops from polished rice to husked rice, beriberi disappeared. I don't know what happened to the secondary infection, but the important fact is that the disease disappeared. I believe that Dr. McGarrison also thinks that goitre is an infectious disease. If we can make pellagra disappear by diet and goitre by iodine it seems to me that it is clouding the issue a little to say that the etiology of the disease is up in the air.

Dr. William M. James. — Like Major Nichols, I wish to place myself on record as to the importance of diet in the etiology of pellagra, without desiring to start any trouble. What pellagra I have seen has convinced me that if unbalanced diet was not the direct etiological factor, it certainly had a great deal to do with it. In the early days of the Canal construction, we had a great many West Indian laborers. These people lived very poorly. Meat was expensive and there was not enough fruit for all. In the cases of pellagra the patients were very badly nourished, and had fever, diarrhoea, sore tongue and mouth, and eruption on their hands and feet, and they died of the disease. It was not so mild as the type Dr. Bass describes. The pathologist, getting the cases, called them ulcerative colitis in a great many instances, and that was exactly what they were.

Dr. Deeks later diagnosed similar cases as pellagra, and this diagnosis was confirmed by many visiting physicians. This was quite a prevalent disease. As the years went by, these cases became fewer and fewer. In my own practice I have seen only one case in the last 5 years, and that patient died.

There has been quite a change in conditions in the matter of diet at the Canal. The population is more stable now and it gets more food with vitamine in it. We see very many cases of other troubles due to unbalanced diet, for our people are excessively fond of carbohydrates. Out of this comes quite a variety of nutritional

troubles—certain cases of eczema and of *retino-choroiditis* and also of beriberi seem to be directly associated with the diet. We see far less beriberi now. It used to be a very common thing, especially among fishermen who lived for several months at a time on the Pearl Islands and who took no meat nor vitamines with them. There is no evidence I can find that in the Canal Zone beriberi was infectious. Twelve or fourteen years ago I could have taken you to the Santo Tomas Hospital and shown you a dozen or more cases of beriberi. We always had 2 or 3 at Ancon, but it is not seen there now. I do not know of any change in the diet in Ancon, but the diet in Santo Tomas has been improved in the last 8 to 10 years.

A singular thing about pellagra is that it was not found among the Panamanians; but if many Panamanians eat an excess of carbohydrates, they also eat a great deal of fruit, as many of my other patients do. In that way they get vitamine also.

In summing up all these facts, I am satisfied that there is an infectious agency that enters into the etiology of pellagra, because the fever and delirium are suggestive of the invasion of an infection, but I look on this as a terminal factor and not as directly due to pellagra itself.

Dr. Roland C. Connor. — My experience with pellagra has been only in Ancon Hospital, and I am exactly in accord with Dr. James's remarks regarding the possible cause of pellagra in our patients; and the course of treatment carried out at Ancon is the one advised by Dr. Deeks, formerly Chief of the Medical Clinic. At present we have very little pellagra in Ancon Hospital, probably 2 or 3 cases a year, and these cases are usually seen in the colored West Indian women. I do not remember having seen a pellagra case in a man for 7 or 8 years.

Most of our cases have been fatal, and I agree with Dr. Bass that we get only the advanced cases, usually when they are in the last stages of the disease. When we get early cases that show slight skin lesions on the hands or knuckles which cause one to suspect pellagra, without extreme emaciation and diarrhoea, relief may be easily obtained by diet; but the cases we usually get are advanced and practically always hopeless. I might say that in some of the latter cases we have had apparently good results from treatment at first, but the patients have relapsed 2 or 3 times and have finally died.

In this connection, I might say that the colored population in the Canal Zone have never been fruit-eaters. They do not give their children orange juice. These children often have rickets and other diseases attributed to malnutrition. They live on a rich carbohydrate diet and eat very little meat, because meat is costly

and fruit is also costly; a *papaya*, — the common fruit of that locality, — costs about 4 to 6 cents a pound. The supply of fruit on the Isthmus is not sufficient; oranges during most of the year cost from 4 to 5 cents apiece, and when imported they cost 6 cents apiece.

Another factor that I should like to have heard Dr. Harris mention in the treatment of pellagra is, whether or not patients are benefited by a change of climate, and whether or not he recommends such a course. For instance, do patients from Alabama who go to one of the states farther north benefit from the effect of the climate? In that connection, I agree with Dr. Bass that transfer of the patient from his home to the hospital may bring about a beneficial result which we may often attribute to diet. All of our patients are put on a high-protein and green-vegetable diet, with plenty of fruit juice, and given dilute nitric acid, 10 to 15 drops well diluted, 2 or 3 times a day before meals. The reason I mention this matter of residence is that I have thought for several years that if I had an American with pellagra I should advise him to leave the Tropics, where he contracted the disease, and go to the Temperate Zone, with the firm belief that he would get well.

Dr. Ernesto Zubieta. — We have very little pellagra in Santo Tomas Hospital. It is not common, and it is not rare. We have an average of 4 or 5 admissions a month, and there are usually 2 or 3 cases in the hospital. I have never seen one case of a native with pellagra. All the pellagra patients are West Indian negroes, and most of them are women. Another point is that about 80% of those women are French West Indians. What causes this condition in this particular kind of people I don't know. We went into their diet, and we found that they eat practically the same thing as the other West Indians and Panamanians.

We also tried to trace their family histories for pellagra and found that a wife might have pellagra and the husband never have it. The cases we have had have been very serious. They come to the hospital when they are vomiting and have bad diarrhoea, and they die from starvation. There is no way to feed them. We had them with diarrhoea with as high as from 20 to 40 stools a day. When cases are not very bad we give them a balanced diet and some of them get well.

Dr. Milton J. Rosenau. — I should like to ask the speaker what his interpretation is of the control of pellagra in asylums and institutions in the the South where Goldberger made his investigations and also the relation of black tongue, in dogs, to pellagra?

Dr. C. R. Edwards. — I have had some experience with pellagra. From 1899 to 1914 I had charge of what is known here as the Union

Poor House. In that Union Poor House, when I left, there were 1,000 inmates and during those 15 years I saw a very large number of cases of pellagra. It is quite certain that at no time during the period of 15 years were we without cases of pellagra, and sometimes we may have had as many as 12 or more. The people who came there suffering from that disease were also sufferers from various other diseases. Some of them were tuberculous, others perhaps were cancerous, others again were suffering from nephritis, but whatever disease they were suffering from they were all in an advanced stage of emaciation, weakness and debility brought about not only by the disease from which they were suffering but also from an advanced stage of starvation. They had not had a sufficient quantity of food for months before.

The cases that I saw were many of them in an advanced stage, and many of them died not from pellagra but from the disease which was producing the debility. Although I have made no microscopical sections of the tissues of these cases — (I have no opportunity of carrying out bacteriological research in these matters, but I have seen the cases and have thought about them a great deal) — it came to my mind that this was not a disease at all, but an expression of disease — that is, a weakness of the nerves which control the nutrition of the skin, *i.e.*, an atrophic condition of the skin brought about by an insufficient nerve control. That is the result of seeing a very large number of cases. If the disease was not too far advanced, patients were fed on a generous diet, with the result that those whose cases were not too advanced recovered in 3 or 4 weeks. The result of my own observations led me to believe that it is not a disease, and not an infectious disease in any sense of the word, but as I said that it is the expression of a disease from lack of nutrition of the nerves which control the nutrition of the skin.

Dr. H. C. Clark. — I can not offer any evidence regarding the etiology of this disease, but I want to discuss briefly the mortality rate of pellagra as we are acquainted with it in the Canal Zone. Dr. Harris states that the disease has an insignificant death rate in the United States. This has not been the case in the Canal Zone. Pellagra, of course, is not among the first 10 diseases that have caused deaths down there, but it does have a rate that is far from insignificant, as I think all our clinical staff will agree. Since 1914 it has been entered as the cause of death in about 1.5% of the autopsies performed at the Board of Health Laboratory. This is about the same as the position held by typhoid fever during the same period of time.

One thing confuses the clinicians and statistical offices in regard to the mortality rate of this disease, and that is the fact that so

many of the cases seem to get entirely well and are lost track of by the attending physicians. A year or so later many of them are taken up for a commission to pass on their sanity, and are then rushed to an insane asylum where very frequently they never get the past medical history of the case, and the patient is discharged under a mental diagnosis in which pellagra is not mentioned. I know this is true, for I have been in a position to follow both the insane-asylum autopsy work and the Ancon Hospital Cases, and have had access to past medical histories. I have seen more than 80 cases of pellagra at autopsy, and all them were in West Indian negroes from 21 to 76 years of age. Practically all of them were in females.

This one fact tends to indicate that it may not be an infectious disease but when one takes a general view of pellagra, and takes into account its serious and delayed effect on the central nervous system, it does warrant the belief that it is an infection. In fact, it can run as long and as silent a course as does syphilis in its tertiary stage.

Dr. Seale Harris (*Closing the Discussion of His Own Paper*). — Dr. Deeks should be credited as being the first in America to suggest an unbalanced diet as the cause of pellagra. About 1910 Dr. Deeks called attention to it at Columbia, South Carolina, at a meeting of the National Conference on Pellagra. He had before that time called attention to an unbalanced diet — that is, high-carbohydrate diet — as being the principal etiological factor in many infections. I wish that all of you would read McHarrison's work, and especially the epitome of his work that was published in the *Journal of the American Medical Association*, January 7, 1922, in which he shows that unbalanced diet predisposes to gastro-intestinal infections of all kinds.

I think it is just as unfortunate to neglect the diet factor in considering the etiology and treatment of pellagra as to stop our researches in trying to prove what is the cause of pellagra. I am firmly convinced, myself, that there is an infection associated with it.

Major Nichols called attention to the fact that there is very little pellagra in the Army. It may be the fact that men in the Army not only have better food, but have better sanitary conditions, and the opportunity to infect food is less. The Siler-MacNeal Commission thought it probable that pellagra is transmitted by the ordinary house fly from infected feces to food of human beings. As to the question of change of climate, I have no doubt it is a good thing, but personally I have had but few cases who have not gotten well, and it has not been necessary to change

their residence. I have had cases of pellagra with toxic delirium for weeks, who did get well and stay well.

There is not only the question of diet in treatment, but drugs should be used as indicated. It was shown by Dr. Clarence Johnson, of Atlanta, that 75% of his pellagra cases who had diarrhoea had a complete absence of hydrochloric acid in their stomach contents, and when an achlorhydria exists, dilute hydrochloric should be given. As to control of outbreaks in institutions, I should say that by increasing the diet, resistance is increased, and, as Dr. Edwards pointed out, improvement in food is followed by a decrease in all infections, particularly tuberculosis, scurvy, and pneumonia, etc. As to black tongue in dogs, I haven't had any experience regarding that.

One thought I wish to bring out especially is this — why has there been a very marked decrease of pellagra in the South? I believe there is not one case now where there were 5 or 10 cases 10 or 15 years ago. So far as I know, there has been no marked improvement in the food conditions among the poor and ignorant classes in the South. There *has* been a very great improvement in sanitary conditions. Typhoid fever, uncinariasis, amoebiasis, have all greatly decreased at the same time that there has been the decrease in pellagra. It seems to me probable that the improvement in sanitary conditions in the South has lessened the chances of the infection of pellagra to spread.

INSULIN

F. G. Banting, M.D.

The purpose of this paper is to give the physician a brief outline of the principles underlying the action and the use of insulin. I have purposely avoided a review of the voluminous literature, because time is wanting. I therefore give you that conception of diabetes which is built upon the innumerable researches of associates past and present, not least among whom was Lepine, of France, whose grandson represents France at this Conference.

In the normal healthy individual, carbohydrates, such as starch and sugar, when taken in the food, are converted into glucose by digestion. In this form it is absorbed into the blood stream. It is then carried to the liver, where it is converted *into*, and stored as, glycogen. As the tissues of the body require glucose, the glycogen stores of the liver are drawn upon. If the supply of carbohydrates greatly exceeds the demand of the tissues, carbohydrates may be converted into *fat* and stored as such. Very small amounts are excreted in the normal urine.

When glucose is absorbed into the blood stream, there is an increased percentage of sugar in the blood, which stimulates the Islands of Langerhans to pour out their secretion. Normal islet cells have a tremendous reserve, and may cause very large amounts of glucose to be metabolized. *When, as in diabetes mellitus*, the functional ability of the islet cell is impaired by nerve strain, infection, changes in blood supply, or over-activity, the extra reserves are found wanting, and sugar, if given in large amounts, remains circulating in the blood stream, in a *higher percentage*, and for *longer periods of time*, than normal. This increased percentage of sugar in the blood is recognized by the kidney and sugar is excreted in the urine. The *hyper*glycæmia thus produced gives rise to excessive *thirst*. The large amount of fluid taken to combat the thirst gives rise to *polyuria*. Since the tissues are undernourished, from failure to burn sugar, there is increased demand for food, as evi-

denced by excessive *hunger*. The increased amount of food throws still greater strain upon the insulin-producing mechanism which is required for its metabolism, and a vicious circle is established which results in rapid emaciation and loss of strength, despite the ingestion of large quantities of food.

Thus the classical symptoms of *diabetes mellitus* are explained. Fats burn only in the fire of carbohydrates. If the progress of such a case is not interrupted by treatment, acidosis occurs. When the rate of production of acetone bodies exceeds the rate of excretion, they accumulate in the system, giving rise to diabetic coma. This cycle is observed in all cases of untreated pancreatic diabetes. In children and young adults the progress is *usually rapidly* fatal. In middle life and old age, the development of the disease is slower.

The fundamental principle underlying dietetic treatment in diabetes, depends upon the administration of the minimum amount of carbohydrate necessary for the maintenance of life, and at the same time upon administering it in such a form that absorption will be so slow that the pancreas can pour forth its secretion in adequate amounts for the normal metabolism of the *given* carbohydrate. Thus, Allen elaborated a system of treatment which consisted of rendering the patients' blood-sugar normal by starvation, and then feeding them upon vegetables and fruit in which the percentage of carbohydrate was very low, protein and fat being added sparingly. Woodyatt, Wilder and others finally evolved a diet in which there was a definite ratio between the carbohydrate, protein and fat.

In order to live, the body requires a certain number of calories. This caloric requirement varies, in different individuals, approximately with the *surface area* of their bodies, their *age*, *sex* and *weight*, and can be calculated by the Dubois chart and the Aub-Dubois table. Roughly speaking, this basal requirement is about 25 calories per kilo of body weight per day. If this requirement is not supplied by the food, it is drawn *from* the tissues of the *individual*. Protein and carbohydrate, when burned in the body, provide 4 calories of heat per gram, while each gram of fat supplies 9 calories of heat. The utmost use should therefore

be made of the fat, but its use is limited by the fact that without carbohydrate it cannot be *completely* oxidized. In the same way the use of protein as a carbohydrate substitute is limited, since 46% of it may produce ketone bodies, and 56% of it *may* be converted into carbohydrate. It has been estimated that the body requires ⅔ of a gram of protein per kilo of body weight per day. The remaining calories must be supplied by carbohydrate and fat in a ratio that will prevent the production of ketone bodies. In order to ascertain the number of grams of the various food substances, many formulæ have been compiled, for example:

M = caloric requirement, ⅔ of the body weight in kilos, gives the protein requirements in grams = P. The carbohydrate, C, and fat, F, requirements are derived from the following formulæ:

$$F = \frac{M}{10} - \frac{P}{2} \qquad C = \frac{M - 10\,P}{30}$$

The simplest is that of Dr. Hipwell, which is as follows:

M = total number of calories required by individual.

(1) 75% of M = calories derived from fat.

(2) 13% of M = calories that must be derived from carbohydrate.

(3) 12% of M = calories that must be derived from protein.

By dividing the protein and carbohydrate calories by 4, and the fat calories by 9, the respective grams of each are obtained. For example, patient weighs 64 kilos:

Minimum caloric requirement was calculated 64 x 25 – 1600 calories.

The diet prescription was as follows:

$$\text{Fat } \frac{75\% \text{ of } 1600}{9} - \frac{1600 \times 0.75}{9} = 133 \text{ grams}$$

$$\text{Carbohydrate } \frac{13\% \text{ of } 1600}{4} = \frac{1600 \times 0.13}{4} = 52 \text{ grams}$$

$$\text{Protein } \frac{12\% \text{ of } 1600}{4} = \frac{1600 \times 0.13}{4} = 48 \text{ grams.}$$

The number of grams of carbohydrate, protein and fat being ascertained, the patient's diet is compiled by the use of food tables.

There is no disease which requires such an intimate *coöperation* between the physician and the patient as *diabetes mellitus*. Patients should be thoroughly instructed in the cause, course and complications of their disease, and should be taught *urinalysis*, the calculation and preparation of a diabetic *diet*, and how to administer their own insulin and to calculate its dose. They should be particularly warned of the prodromal symptoms and treatment of *overdosage*. It is impossible and impracticable for a physician to treat and teach the patient except in a hospital where, in addition to an accurately dispensed diet description, daily urinalysis of the 24-hour specimen for volume, specific gravity, reaction, albumen, acetone, and qualitative and quantitative sugar, may be effected. The estimation of blood-sugar is desirable, but not absolutely imperative if the urinary sugar is closely followed.

When the patient presents himself for treatment, a careful *history* is taken and a *complete physical examination* is made. Special attention is directed to the finding of a possible *focus of infection* — tonsils, teeth, sinuses, chest, and digestive system are examined clinically, as well as by X-ray. Special consideration is given to biliary tract infection, constipation, and chronic appendicitis. If any source of septic absorption is located, it is *appropriately* treated, since such condition may lower and unstablize carbohydrate tolerance.

The patient is placed upon a diet, the caloric value of which is calculated on his basal requirement, and is maintained on it for 3 or 4 days, or until the urine is sugar-free. The quantity of sugar excreted is estimated daily, and this amount, subtracted from the available carbohydrate ingested, gives *approximately* the utilization. The available carbohydrate includes 56% of the protein, 10% of the fat, and the total carbohydrate in the diet. It may be noted that when a patient is placed upon a diet in which the protein, fat and carbohydrates are *balanced*, the amount of sugar excreted daily soon approaches a fairly constant amount; whereas, if the diet is not well adjusted to the patient's requirements, there is wide variation in the amounts of sugar excreted.

If a patient becomes sugar-free and "blood-sugar-normal" on a basal requirement diet, the *caloric intake* is *gradually*

increased until sugar appears in the urine. The tolerance is thus ascertained. If a patient remains sugar-free and has a normal blood-sugar when *on* a diet containing 700 calories above his basal requirement, the case is not considered sufficiently severe for insulin treatment, since 700 calories over and above his basal requirement are sufficient for the needs of his daily activities. If, however, he is unable to metabolize this amount, insulin treatment is commenced.

Diabetes mellitus is due to a deficiency of the internal secretion of the pancreas. The main principle of treatment is, therefore, to correct this deficiency. If it is found that the patient is unable to keep sugar-free on a diet that is compatible with an active, useful life, sufficient insulin is administered to meet this requirement.

The initial dose of insulin should not be more than 5 units twice a day. This amount can be gradually increased until the patient becomes sugar-free, the diet being kept constant. It may be roughly estimated that each unit of insulin causes from 1½ to 2½ grams of carbohydrate to be utilized. The amount of utilization per unit of insulin is less in severe cases with high blood-sugar and during the course of infection, and is greater in mild cases. The *time* of administration of insulin is an important factor. It is best given from 20 minutes to ½ hour before the morning and evening meals, so that the curve of *hypo*glycæmia produced by the insulin is just *superimposed upon, and counterbalances* the curve of *hyper*glycæmia produced by the meal. A larger dose is usually given before breakfast, so that the noon meal is also cared for. For example, if a patient is receiving 25 units of insulin per day, 15 units would be administered in the morning dose, and 10 units in the evening. When the *dose of insulin* and *diet* are balanced so that the patient's blood-sugar is normal, they are concurrently increased until the required amount of food is reached. Insulin is given hypodermically, since other means of administration have been found unsatisfactory.

When a patient is given too large a dose of insulin the blood-sugar falls below its normal level, producing marked reaction, which begins in from *one and a half* to *six hours* after the patient receives the overdose. The average time is *three to four hours*. The interval varies with the individual,

the dosage, and the food ingested. The first warning of this *hypo*glycæmic reaction is an *unaccountable anxiety* and a feeling of impending trouble, associated with *restlessness*. This is frequently followed by *profuse perspiration*. The development of this symptom is not affected by atmospheric conditions, and is independent of physical or mental activity.

At this time there is usually a great desire for food. Very soon the patient will notice a certain sensation as of *clonic tremor* in the muscles of the extremities. This can be controlled at first. Coördination, however, is impaired for the more delicate movements. Coincident with this, there is a marked *pallor* of the skin with a rise in *pulse rate* to one hundred or *one hundred and twenty* beats per minute. Pupils become dilated. The blood pressure falls about 15 to 25 millimeters of mercury, and patient feels faint. The ability to do physical or mental work is greatly impaired. In a severe reaction there may be a considerable degree of *aphasia*, the patient having to grope for words. The *memory* of names and figures may be quite faulty. As the blood-sugar falls to a still lower level, the blood pressure and body temperature also fall and *collapse*, *unconsciousness*, *convulsions*, *and finally death*, may occur.

The *onset* of hypoglycæmic symptoms depends, not only on the *extent*, but also on the *rapidity* of fall, in blood-sugar. The level at which symptoms occur is higher in the diabetic with marked hypoglycæmia, than in a patient whose blood-sugar is normal. A hypoglycæmic reaction, when once experienced by a patient, is rapidly recognized on following occasions. Consequently it is safer for every patient, before leaving the hospital, to have experienced the sensations of an overdose.

The ingestion of carbohydrate in the form of orange juice (4 to 8 ounces), glucose or candy, relieves these symptoms in from 5 to 10 minutes. If untreated, and coma or convulsions have occurred, 10 to 15 minims of *epinephrin* will usually restore consciousness within 3 minutes, at which time glucose should be given by mouth to prevent further recurrence.

The ability of the severe diabetic to burn glucose is markedly impaired,— therefore the excess of fat is incompletely oxidized, giving rise to ketone bodies. These appear

in the blood and urine as acetone and diacetic and betaoxybutyric acids. Insulin causes increased carbohydrate metabolism, and consequently fats are completely burned. This is substantiated by the fact that acetone and sugar disappear from the urine almost simultaneously, following adequate amounts of insulin.

When the *production* of acetone bodies is more rapid than the *excretion*, they accumulate in the blood, giving rise to air-hunger, drowsiness, and coma. The need of insulin is then imperative. After its administration, the utilization of carbohydrate by the body gives complete combustion of the fats.

When a patient is admitted to hospital in diabetic coma, the blood and urinary-sugar and acetone estimations are made as soon as possible. (The urine is obtained by catheterization if necessary.) While these tests are being carried out, the large bowel is evacuated with copious *enemata*. If sugar and acetone are present in large amounts in the urine, from 30 to 50 units of insulin are given subcutaneously immediately. Blood and urinary-sugar should be frequently estimated, because of the danger of hypoglycæmia. To prevent this, from 30 to 50 grams of glucose in 10% solution may be given intravenously or by rectum. If the patient is profoundly comatose the insulin may be administered intravenously with the glucose.

The patient usually regains consciousness in from 3 to 6 hours. From this time on fluids and glucose may be administered by mouth, *if retained*. The patient should be urged to take at least *200 cubic centimeters* of fluid per hour. In from 8 to 10 hours the ketone bodies are markedly reduced.

On the following day protein may be given every 4 hours, *as* the white of one egg in 200 cubic centimeters of orange juice. In 2 to 3 days, when ketone bodies have disappeared from the urine, fat is cautiously added, and the patient is slowly raised to a basal requirement diet. He is then treated as an ordinary diabetic. During the period of coma, the patient is kept warm and toxic materials are eliminated from the bowel by purgation and repeated *enemata*. A large amount of fluid is given to dilute the toxic bodies and promote their elimination. This may be administered

intravenously, subcutaneously, or per rectum. If signs of circulatory failure develop, these are treated by appropriate stimulation.

Striking results have been obtained with the above procedure. However, it has been found that the longer the period of untreated coma, the more *grave* is the prognosis and the slower the recovery, if it occurs. Cases complicated by severe infection, gangrene, pneumonia, or intestinal intoxication may recover from acidosis and coma, but succumb to the complication.

In the diabetic with *tuberculosis*, insulin enables the use of proper nourishment to combat the tubercle infection. Patients formerly considered *bad surgical risks*, if given proper dietetic treatment with insulin may be protected from the acidosis, hyperglycæmia, and glycosuria which otherwise usually result from the anæsthetic. Diabetic infections such as boils, carbuncles, and gangrene, and also intercurrent infections such as bronchitis, influenza, and fevers, are favorably influenced by the normal blood-sugar and increased metabolism which the administration of insulin permits.

Regardless of the severity of the disease, it has been found that by carefully adjusting the *diet and the dose of insulin, all patients may be maintained sugar-free.* Since this is possible, it is to be strongly advocated, because we have abundant evidence for the belief that there is *regeneration of the islet cells of the pancreas* when the strain thrown upon them by a high blood-sugar is relieved. The *increase in tolerance* is evidenced by the *decreasing dosage of artificially administered insulin. In fact, in some moderately severe cases*, the tolerance has increased sufficiently so that they no longer require insulin.

Diabetes mellitus may be considered fundamentally as a *disordered metabolism, primarily of carbohydrates*, and *secondarily of protein and fat.* It is indisputably proved that for normal metabolism of carbohydrate in the body, adequate amounts of insulin are essential. It follows, therefore, that the treatment consists in giving just sufficient insulin to make up for the deficiency in the patient's pancreas.

Insulin enables the severe diabetic to burn carbohydrate, as shown by the rise in the respiratory quotient following the

administration of glucose and insulin. It permits glucose to be stored as glycogen in the liver for future use. The burning of carbohydrate enables the complete oxidation of fats, and acidosis disappears. The normality of blood-sugar relieves the depressing thirst, and consequently there is a diminished intake and output of fluid. Since the tissue cells are properly nourished by the increased diet, there is no longer the constant calling for food,— hence *hunger-pain* of the severe diabetic is replaced by *normal appetite.* With the increased caloric intake, the patients *gain rapidly in strength and weight.* With the relief of the symptoms of their disease, and with the increased strength and vigor resulting from the increased diet, *the pessimistic, melancholy diabetic becomes optimistic and cheerful.*

Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrate, so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.

DISCUSSION

Sir Thomas Oliver (*Opening the Discussion*).— I must admit that I am quite taken aback at being called upon to introduce the discussion. I have listened with very great pleasure to what Dr. Banting has told us, and I am glad that at the outset he recognized the high-class character of the work done, by paying a well-deserved compliment to the grandfather of one of the members present, Dr. Lepine.

Dr. Banting has introduced a method of treating diabetes which has "caught on." At the close of his lecture he told us that insulin is not so much a cure for diabetes as it is a method of treatment. The treatment of diabetes has become such a scientific matter that for the last year or two I have handed over the care of my own cases of the disease to the younger men of the profession, who are more intimate with new methods of treatment than I am.

In addition to careful observation as regards diet, there are required examination of the urine and examination of blood-sugar, etc. Nothing could exceed the graphic picture which Dr. Banting drew for us this afternoon of the effects, both of abnormal deficiency, and of excess of sugar in the blood. He pointed out the dangers of acidosis, and how this too may be treated. I know of no method of treatment which has so captured the spirit of the times as that which Dr. Banting has introduced. We were at a

loss to know what to do with diabetes. Progress in regard to it had been slow. Dr. Banting has shown the way. It was helpful to hear from him that even although in diabetes, as a consequence of the prolonged strain associated with carbohydrate metabolism, the Islands of Langerhans degenerated, yet they are capable of being regenerated.

I cannot go into all the chemical details to which Dr. Banting has drawn attention. Surgeons have been disposed to taunt physicians and say: — "What progress has been made in medicine during the last few years? See what we are doing to save life by our wonderful operations!" We can at least reply that one of the greatest contributions of modern times is that of Dr. Banting. But for it, even many surgical operations would be impossible. The story of his work is familiar to most of you.

I should like to say that we have had an address which deals with a subject of enduring interest. That story has been told in a quiet and unostentatious manner, and with that simplicity of mind and character which both riveted our attention and won our hearts,— and just as he has gained the appreciation of this audience, so has he secured the gratitude of diabetic patients all the world over.

Dr. Milton J. Rosenau.— I have had no personal or clinical experience with diabetes. It is not often given to a group of men to listen to epoch-making experiences which have come from the hands and minds of genius. That has been our privilege today in listening to Dr. Banting tell of his splendid work which is doing so much for mankind.

Dr. Seale Harris.— Dr. Banting not only has made one of the greatest contributions in the history of medicine, but he has the rare faculty of applying the scientific work that he has done. I have heard Dr. Joslin, Dr. Allen, and many others talk on the treatment of diabetes, but the paper of Dr. Banting which you have heard today is the simplest and the most practical discussion of the subject of treatment of diabetes by insulin that I have ever heard.

It is not a difficult thing to treat diabetes with insulin. Indeed, it is a simple thing. Any physician can learn in a few days how to treat the average cases; and not only that, but every general practitioner should know how to treat diabetes, and particularly coma, because the family physician is the first to see the case of diabetes, and the last. If he does not know how to treat coma, many cases will die before they can be gotten to a hospital.

Our experience with insulin has covered more than 100 cases of diabetes in the last 18 months. Out of that number, there were

8 or 9 cases of coma, every one of which would have died had it not been treated with insulin. One case of coma died because the patient was moribund when he entered the hospital; 6 or 7 cases of gangrene have been brought to our clinic and probably would have lost their legs, had it not been for the use of insulin. Some cases of gangrene yielded simply to the use of insulin. I had never seen a case of gangrene yield to medical treatment before we had insulin. We have had a number of cases of severe diabetes that certainly would have died without insulin. The use of insulin enables the surgeon to operate on a diabetic patient with as much safety as if that patient did not have diabetes.

The treatment that Dr. Banting has outlined is perfectly simple and can be learned by any physician, as I have said. Dr. Banting was good enough to come to us at our clinic in Birmingham, and to give several talks to a number of general practitioners who gathered for the purpose of learning how to use insulin. We have heard since from many of these practitioners, and they are treating their diabetic patients successfully with insulin.

In our clinic in Birmingham we have made some studies on hyperinsulinism and dysinsulinism which may interest the members of the conference. The results of those studies were reported at the recent meeting of the American Medical Association.

HYPERINSULINISM AND DYSINSULINISM

Diabetes, of which hyperglycæmia is a manifestation, is essentially a condition due to a deficient secretion of insulin by the "Islands of Langerhans"; and, according to modern medical nomenclature, it should be called hypoinsulinism. Diabetes, or hypoinsulinism, therefore, bears the same relation to the internal secretion of the pancreas that myxedema, or cretinism (hypothyroidism) bears to that of the thyroid gland.

We know that hypothyroidism is not the only dysfunction of the thyroid gland, and that there is a hypersecretion of that important organ — hyperthyroidism — in which there are certain characteristic symptoms, i.e., the syndrome, called hyperthyroidism, and also known as Graves' disease. It has been observed that hyperthyroidism sometimes precedes hypothyroidism. It seems probable that there are other dysfunctions of the Islands of Langerhans, besides hypoinsulinism, and that an excessive formation of insulin may occur. Hyperinsulinism should produce definite results, i.e., a reduction in blood-sugar, which, when below a certain limit — usually about 0.070 — brings on characteristic symptoms, now known as the insulin reaction. It also seems probable that a deficiency of the secretion of insulin may follow

prolonged excessive work of the Islands of Langerhans, just as in other glands, or organs, hypertrophy and hyperactivity may be followed by degeneration, atrophy and loss of function.

It was the above line of reasoning that caused me to think that there may be such a condition as hyperinsulinism, and when I saw the insulin reaction in diabetics, I realized that I had seen many non-diabetic patients who had complained of the same symptoms, i.e., hunger, weakness and the anxiety neuroses. I mentioned this to Dr. Banting while on a visit to the Diabetic Clinic in the Toronto General Hospital, in March, 1923, and asked him if he or others had observed an excessive secretion of insulin in laboratory animals or human beings. He said that they had done nothing along that line; and that he had seen nothing in medical literature on the subject.

Knowing the amount of food ingested at a given time, by means of blood-sugar determinations we are able to estimate with some accuracy the degree of insulin secretion; particularly, since we know that by the administration of insulin, hypodermatically, the amount of sugar in the blood may be reduced to any level, according to the number of units administered and the amounts of glucose-forming food ingested. It therefore seemed probable that, since hypoglycæmia is the result of hyperinsulinemia, a study of the blood-sugar in patients who have symptoms of hyperinsulinism should show readings of below 0.070 (70 milligrams per 100 c.c. of blood).

The first patient, a physician, who presented symptoms of hyperinsulinism, consulted us on March 19, 1923, saying that every day about one hour before his noon meal he felt weak, nervous and so hungry that he could not work. He had found that he would get relief from taking candy, or a soft drink, or from drinking milk, eating fruit, or from eating anything. It was then about an hour before his time for luncheon, and a specimen of blood was obtained for the determination of its sugar content. It was found to be 0.065 (or 65 milligrams per 100 c.c. of blood). On another occasion, May 15, 1923, the same hour, his blood-sugar was 0.070. This patient had no other symptoms except that he had been over-weight and had lost about 25 pounds. His blood pressure was low, systolic 95, diastolic 60. A well-balanced diet was given him, with instructions to take food of some kind every 3 hours. A year later this physician-patient told me that he had been feeling well since he had been taking food 5 times a day.

On October 4, 1923, a patient, who had been under observation at times for various digestive troubles for 7 years, complained, in

his own words—"I get so hungry and weak every day about an hour before meals that I feel like I will die if I do not eat something. I believe that I would die if I had to go 2 or 3 hours past mealtime without anything to eat. Eating anything always relieves me and I am comfortable for 3 or 4 hours after meals." He was told to wait in the office to let us see him at a time when he was having the symptoms of which he complained. His blood-sugar was 0.065 at 12:00 M. He was told to eat a full meal and come back 2 hours later. His blood-sugar was then 0.130. A glucose tolerance test (100 grams of glucose) was given him, with the following blood-sugar readings and urinary findings:

Time	Blood-Sugar	Urine Test
12:15 P.M.	.098	No sugar
12:45 P.M.	.116	No sugar
1:15 P.M.	.167	Trace sugar
2:30 P.M.	.135	No sugar
3:30 P.M.	.067	Trace sugar

This patient lived in a suburb, about an hour's ride by trolley, and, after the glucose tolerance-test, went home without eating anything. He said that before he reached the end of his trolley ride he was so weak that he could hardly walk, and that it was only with great effort that he was able to get home. He said he thought he would die before his wife could get him something to eat, and he felt so faint that he could hardly eat; but that he felt all right after eating. Since his last blood-sugar reading, at 3:30, 2 hours before he had food, was .067, it was probably much lower when he had the severe hypoglycæmic reaction. In this case the glucose seemed to have stimulated the secretion of insulin, which continued after the glucose had been disposed of. There also seems to be a lowered glucose tolerance in this case, probably a dysinsulinism, in a patient who is a potential diabetic.

On January 23, 1924, a married woman, aged 39, with a history of a transient glycosuria on 2 occasions in the previous 18 months, presented marked symptoms of hypoglycæmia without having had insulin. She had been over-weight, having weighed 220 pounds, when a trace of sugar was first found in her urine, in the summer of 1922. She was then placed on a low-fat, low-carbohydrate diet, and reduced to 160 pounds, but her health had become impaired during that time. One striking symptom of which she complained was, in her own words: "I awaken at from 12 to 2 at night with a nervous rigor, or quivering, very weak, disturbed feeling, cold extremities, and am hungry. Eating an orange relieves me." She also complained of the "nervous rigors" when her stomach was empty during the day.

A blood-sugar was ordered taken during one of these nervous rigors, and it was found to be 0.047. (The lethal low blood-sugar point in rabbits is 0.040.) Two hours after she had had 25 gms. of glucose, her blood-sugar was 0.130. This patient presented symptoms of both hyper- and hypo-insulinism, apparently a dysinsulinism analogous to patients showing evidences of both hyperthyroidism and myxedema. This patient had no sugar in her urine at any time during her 6 weeks' stay in the infirmary, though, since her family physician is a careful, well-prepared physician, I do not question her having had glycosuria when she weighed 220 pounds, and she was no doubt eating an excess of glucose-forming foods. (A detailed report of these 3 cases will be given with the complete histories of other cases that we believe had hyperinsulinism.)

The above 3 cases show symptoms of hyperinsulinemia and, with blood-sugar findings below 0.070, stimulated us to undertake further studies of the blood-sugar at the fasting period in non-diabetics. Since that time blood-sugars have been made a routine in the examination of all patients.

It should be remembered that all our patients come to us for treatment of some gastro-intestinal or nutritional disturbance, and all of this series were ambulatory cases, though some of them were sent to the infirmary for rest, diet and general observation. Blood-sugar determinations were made in 253 cases, 92 of which were diabetics who showed varying degrees of hypoglycæmia. Of the 169 cases, 12 had blood-sugar readings of below 0.070 in specimens obtained during the fasting period; and all of these, with 2 or 3 exceptions, had symptoms that could result from hypoglycæmia. The blood-sugar determinations were made by Dr. W. S. Geddes, or under his direction. The Folin-Wu method was used.

The question as to whether these low blood-sugar readings were due to a lack of food, or to a hyperinsulinemia was considered. If it were due to a lack of food, the starving patient should show a low blood-sugar. We chanced to have had 4 patients who were literally starving to death; 3 were cases of carcinoma, with almost complete occlusion of the esophagus. All 3 patients were very much emaciated and had been able to take almost no food for several days or weeks before they came to us. None of them gave a history of symptoms of hypoglycæmia. The blood-sugar readings of these 3 patients were as follows: 0.090; 0.084; and 0.090.

We also had a patient who had almost complete stenosis of the pylorus, due to tumor, ulcer of carcinoma, of the pyloric end of the stomach. The X-ray showed 90% retention of the barium

meal in 6 hours, and 75% retention in 24 hours. This patient had vomited practically everything she had eaten, for weeks, and was in a state of marked emaciation. Her blood-sugar was 0.079.

It seems that in cases of starvation the amount of sugar in the blood is kept within the normal range by endogenous catabolism. There is some evidence to show that patients with carcinoma have reduced carbohydrate tolerance; but even so, in these cases the amount of glucose derived probably from the protein of the patients' own tissues, was sufficient to keep the blood-sugar above the point where hypoglycæmic reactions occur. Since in the starvation cases the blood-sugars were within the low normal range, and none of the 4 patients had symptoms of hypoglycæmia, and the patients having blood-sugars below 0.070 with few exceptions had symptoms of an overdose of insulin,— it surely seems that there is such a condition as hyperinsulinism.

CONCLUSIONS

1. Hyperinsulinism is a condition, perhaps a disease entity, with definite symptoms, i.e., those described as being due to hypoglycæmia.

2. It seems probable that one of the causes of hyperinsulinism is the excessive ingestion of glucose-forming foods, and that as the result of over-activity induced by over-eating the Islands of Langerhans become exhausted and hypoinsulinism (diabetes) follows. It is possible that the hunger incident to hyperinsulinism may be a cause of over-eating, and, therefore, of the obesity that so often precedes diabetes.

3. It seems probable that dysinsulinism, either an increase or a decrease in the secretion of insulin, may follow infection or trauma of the pancreas.

4. Since excessive hunger is a symptom of hypoglycæmia, it may be that normal hunger is the call for glucose, and that it may be in part or wholly of pancreatic origin, and not entirely an expression of an empty stomach. It is also possible that, associated with ulcer of the stomach or duodenum, there may be a co-existing disorder of the pancreas, and that the frequent feedings which give relief in ulcer may do so by supplying the glucose to meet the needs of over-functioning Islands of Langerhans. In one case of ulcer we found a low blood-sugar.

5. Since blood-pressure readings have been low in all except 2 of the non-diabetic patients who have had symptoms of hypoglycæmia, it seems possible that hypoadrenalism may be associated

with hyperinsulinism. It also seems probable that secretory disorders of the Islands of Langerhans may be associated with dysfunctions of the thyroid, the pituitary bodies and other organs of internal secretion.

6. Fractional tests of gastric secretions after the Ewald meal have been made in several non-diabetics having symptoms of hyperinsulinism,— with variable results, so that there is no apparent relation of secretory disorders of the stomach to pancreatic dysfunction.

7. No studies of the external secretion of the pancreas were made in these cases. It seems probable, however, that since a chronic pancreatitis is likely a cause of dysinsulinism, the glands secreting trypsin, amylopsin and steapsin are often involved, with either increased or decreased function.

THE CAUSATION OF CANCER

W. Arbuthnot Lane, M.S.

When I received an invitation to attend this Congress, I realized at once that I was not expected to display any very intimate knowledge of the diseases which affect the inhabitants of the Tropics. A moment's consideration convinced me that it was hoped that I might be able to suggest some means by which the inhabitants of these regions might be protected as much as possible from the harmful influences which the association with a white population must necessarily exert on them.

I have heard frequently of the White Man's Burden, but I am more familiar with and more interested in the black man's burden. The native of the Tropics living in his normal surroundings leads a very happy existence, in the full enjoyment of the pleasures of life. His very smile suggests a cheerful disposition and a happy outlook on life generally. He may not infrequently have circulating through the several tissues of his body a great variety of organisms, usually in the form of minute worms. In the vast majority of cases he suffers very little, if any, inconvenience from their presence; hence they do not interfere materially with his activity or with the satisfaction of his appetites.

Occasionally, as in the case of yellow fever, cholera, dysentery, etc., such organisms are very virulent and may terminate his existence in a few days, in a manner which is usually almost painless. The study of these organisms has afforded endless occupation and interest to researchers of other races, who display much ingenuity, skill and classical knowledge in describing their habits and in supplying a nomenclature for them.

What does the association with the white man do for the native? The native only too readily imitates the universally faulty diet and habits of the white man. In consequence, he of necessity acquires the abnormal conditions and the diseases resulting from this intimate and unfortunate rela-

tionship with the white man which has been forced upon him. He becomes constipated; he suffers from a variety of infections of his gastro-intestinal tract; he becomes bilious, depressed and miserable; he may suffer severe abdominal pains or discomfort; he gets ulcers in his stomach and intestines; his appendix becomes inflamed and perhaps gangrenous, and his tissues are saturated with poisons which circulate in his blood, and which are derived from the infections of his intestinal contents. Finally that dread scourge of civilization, cancer, attacks the poor black man with a frequency proportionate to the degree of his civilization.

Can any of the troubles of savage life be compared to the very prolonged misery of death from cancer, fearful enough when it affects man, but infinitely more disgusting and hateful when it attacks the woman?

Such is the appalling price the native pays for civilization. I feel that I can perhaps but fulfill your wishes if I read you a short paper on cancer, after which I trust you will afford me your sympathetic suggestions as to the best means to be adopted to safeguard the poor native, as far as is possible in the circumstances, from the misery, loss of health, disease and death which result from his enforced association with his white brother. Also, let us consider how much we can learn, from this study, of any means we can adopt to diminish or eradicate this ghastly disease from civilized races,— a disease which is increasing with a terrifying frequency. It is the biggest problem before us at the present moment, and one which we must solve with all the skill, ability and knowledge at our disposal.

I have spent the last 25 years in the study of the causation of chronic intestinal stasis and of its consequences, and I propose to state as briefly as I can the conclusions at which I have arrived, and the method by which these morbid conditions can be obviated.

I employ the term chronic intestinal stasis to indicate an abnormal delay of the intestinal contents in any portion of the gastro-intestinal tract. This stagnation produces two definite series of changes: *the primary*, which are mechanical; and *the secondary* which are toxic, and result from what is commonly called intestinal auto-intoxication.

I have no doubt that the primary accumulation of the intestinal contents in the canal is due to defective nutrition. In the first instance, the food of the mother during pregnancy, and particularly during lactation, affects most materially the vitality of the nerve and muscle fibres of the intestinal wall of the infant, as well as of the mother. It frequently results in the inability of the mother to produce enough milk to nourish her child.

In the case of people leading a primitive existence, should this inability arise, the child soon dies, since there is no efficient substitute for the mother's milk.

In civilized communities, owing to the imperfect nutrition of the mother, this inability to provide the normal diet for the child is only too frequent.

To meet this, the child is fed with artificial substitutes, which, with the exception of cow's milk, replace very imperfectly — and too often very deleteriously — the natural food which a healthy mother should produce. Even in the case of cow's milk, its usefulness is commonly diminished or even destroyed by imperfect feeding of the cows, by heating the milk, or by the addition of alkalis, antiseptics, water or other substances.

During lactation the child's intestines may suffer because of the imperfect nutrition of the mother, and the consequent deficiency of her milk in important components.

While the child is wearing napkins, however defective the milk of the mother or that of the artificial substitutes for it, the bowels are usually evacuated at frequent intervals. When the napkin is discarded the mother or nurse then proceeds to regulate the action of the child's intestines. This means that the child is taught to have a single formed action daily, which in civilized life is regarded as the normal and as being sufficient for the needs of the individual.

Consequently what was food — but what is food no longer — is retained in the bowel for an excessive period, the child being constipated for twenty-four hours. This habit, which in the first instance is adopted probably to insure cleanliness and also to save trouble, is continued throughout the whole of life and a single formed motion is the aim of everyone who wishes to consider that the best possible is being done to ensure health. But little importance is laid

upon this rule, and in consequence the stagnation of the intestinal contents becomes an increasing anxiety to the more thoughtful members of the community. This is evidenced by the enormous fortunes that have been made by the sale of purgatives.

The capacity to evacuate the contents of the bowel is progressively diminished by the formation of acquired bands. The earliest to form I call the *first and last kink.*

In the first instance these bands are evolved to support the loaded bowel, but later they constrict the bowel at points situated at increasing distances from its termination. These obstructions produce in the stomach and small intestines changes which are chiefly mechanical in their causation. In a subject whose vitality is too poor to permit of the formation of controlling-bands to support the intestine — the function of whose wall is diminished by imperfect nutrition — the large bowel not being efficiently anchored by these evolutionary structures dilates, prolapses and elongates, its lower end especially puddling in the pelvis and affording in advanced cases an almost insuperable obstacle to the passage through it of hard fœcal matter.

All these troubles are produced and accentuated by the diet of civilization, which is deprived of most that is useful and necessary for nutrition, and of that roughage which, being incapable of digestion, forms the bulk which stimulates the action of the muscle fibre of the intestine. On the other hand, the food which is consumed is made up of material concentrated in quantity, which looks nice and which appeals to the palate. Contrast this with the diet and habits of the native leading a primitive life:—

His food is very simple and contains all the ingredients necessary to nutrition, to the normal functioning of the gastro-intestinal tract and to perfect health.

His habits differ in no way from that of other animals in their normal habitat. Like them he evacuates the contents of his bowel 2, 3 or more times a day after taking food and in proportion to its amount, and the character of the motion is soft and formless.

The attitude assumed in the process of its evacuation is the squatting posture which, for obvious reasons, is the most effective for the purpose.

Take this native from his normal surroundings, and make his food and habits similar to those of the members of the civilized community in which he is placed, and he will develop the same changes that take place in *them*, in proportion to the extent to which he acquires their habits and their diet, and proportionately to the duration of his stay among them. It is absolutely certain that, owing to the perfect functioning of his stomach and intestines because of his simple diet, the native in his normal surroundings does not suffer from indigestion, appendicitis, colitis, gastric or duodenal ulcerations, or from cancer of the gastro-intestinal tract or any organ in his body; nor is he subject to the many degenerations of the several tissues and organs of the body, all of which are in effect symptoms of chronic intestinal stasis and not independent diseases.

It is only when the vitality of the tissues is sufficiently depreciated by the poisons which are absorbed from the infected intestinal contents and are circulated through the body, that cancer is ever developed. The seat of the development of cancer is determined in the case of the gastro-intestinal tract by very obvious and simple mechanical causes, which are the result of evolutionary efforts on the part of the organism to meet the disabilities which arise from imperfect nutrition and from abnormal habits.

That the vast bulk of cancer is inseparable from the other results of chronic intestinal stasis, is in my opinion indisputable. The toxic factor produces such a degenerative change in every organ or tissue that its vitality is lowered and its resisting power to the invasion of the organism or other factor which determines the development of cancer, is depreciated. When the organ or tissue has undergone sufficient degenerative change, cancer develops in it. *Cancer never obtains a foothold in a healthy organ or tissue*, and for that reason it exists almost solely in middle or late life.

Aniline cancer, tar cancer, soot cancer, Kangra cancer, etc., develop only after continuous absorption over a period of 15, 20 or more years. In view of the fact that all the known chemical cancers appear only after a very considerable length of time, we are entitled to conclude that all forms of cancer require decades for their development. We cannot be surprised that those who have suffered from in-

testinal stasis and auto-intoxication for a similar period develop cancer.

Cancer is the result of chronic poisoning of the tissues of the body, and, in the vast majority of cases, by the poisons absorbed from the gastro-intestinal tract. The same degeneration of the tissues may be produced by the very prolonged action of X-Rays and chemical poisons. There are hundreds of cases on record, of people having contracted X-Ray cancer and arsenic cancer. Syphilis also effects a degenerative influence on all the tissues of the body and so materially assists in the development of cancer. It is interesting to note the varying effects of the syphilitic virus in the native and in civilized man. Stasis plays a very important part in the manifestations of syphilis and should also be taken account of in its treatment.

Our only hope of preventing cancer is by obviating the development of chronic intestinal stasis and of all its manifestations and results. Cancer is only one of the consequences of stasis but it is infinitely the most incurable and fatal.

The prevention of cancer can be brought about only by a complete revolution in our diet and habits. We must eat food of such a character as will obtain for us the same results that exist in man leading a primitive life. We must discard those foods of civilization which are deprived of vitamines and of the several other important components which are present in natural foods. The public must be educated in the knowledge of food, and must be impressed with its importance. I am certain that they will be keenly interested in the subject, when they learn the explanation of the causes which bring about so much illness, misery and death, and recognize the far-reaching results of those causes. They will then realize that within one or two generations it will be possible to prevent the existence of chronic intestinal stasis and of the consequent intestinal auto-intoxication leading to the development of those morbid conditions which so seriously affect humanity because of the depreciation in vitality produced by those conditions of diet and habit which are at present inseparable from civilization.

We must employ every means in our power to educate the public by literary efforts, by propaganda in the news-

papers, by the formation of societies to distribute information among every class, and by demonstrating in the clearest and simplest possible way how the community can be fed on a natural diet in the cheapest manner, while at the same time a population physically approximating the savage in health and physique and in the freedom from gastro-intestinal affections, cancer, etc., will grow up and will replace the miserable specimens of humanity which form a large proportion of the inhabitants of civilized countries.

A great service is being effected by a book written by that keen and practical writer, Mr. Ellis Barker, entitled "Cancer, How It Is Caused, How It Is Prevented." It has been published simultaneously in England and America. Mr. Barker has the great advantage of having studied the subject with a mind void of bias, and uninfluenced by the creed and education of the medical man, and he speaks to the public in a language which, being free from technical terms, is readily understood by them.

It is most unfortunate that such an improvement in the diet of the people as will ensure health and freedom from disease, must necessarily run counter to custom and to vested interests. In this matter the Health Department of the State may develop sufficient courage and intelligence to interfere in the interest of the members of the community, and may prevent the supply to the public of an enormous amount of food which has been deprived of its most important and useful constituents by mechanical or chemical means. It is a source of great profit to those who manufacture it, and to those people who make a living out of its advertisement.

The difficulties that must be met in supplying the public with such food as will keep them in health and prevent disease are very great indeed, since there is a craving on the part of the so-called civilized subjects for food that is varied in character, that looks nice, and that is easy and pleasant to eat. These obstacles will be overcome only with time. However, I feel that education alone will do a great deal to overcome them, and new habits will be developed and acquired when the immense advantages that such habits afford are realized.

At the present time we have many large philanthropic

societies employing a vast number of intelligent people, most of whom give their services, in the cause of the sick poor. By educating these workers in the knowledge of such diets and habits as will guarantee health and freedom from disease, these societies can broadcast the information necessary for the ensurance of health among the homes of our less fortunate brethren. By doing this effectually, these members will sooner or later destroy the necessity for the existence of the philanthropic body of which they form a part, by eliminating the diseases, the symptoms of which they are endeavouring to alleviate.

The food question is infinitely the greatest and most important problem of the present day, since it concerns so materially the health and happiness of the community; and if properly dealt with, it must result in the disappearance of the vast bulk of the disease, misery and death which is exacting from the community an ever increasing toll.

Before ending these remarks I would particularly call attention to the magnificent statistical work — especially in relation to cancer — which has been carried out by Dr. Hoffman, and with which we are all familiar. It forms a reliable and sound basis upon which much research has been, and I trust will be, founded by other workers. It would be difficult to exaggerate its importance, and we are all very grateful to him for it.

I would also desire to express the very warm appreciation which I am sure is felt by every member of this Conference, of the wonderful work in the prevention of the diseases of civilization that is being effected by the United Fruit Company, in bringing to Great Britain and to the United States a steadily increasing quantity of fresh fruit containing just the most important constituents that are so extremely efficacious in counteracting the development of cancer and all the other diseases which affect us because of our hopelessly deleterious diet and habits.

The United Fruit Company is teaching the community that the eating of fresh fruit is to be regarded not as a luxury, but as a necessity to a healthy existence.

We hope that the Company may be able to increase enormously its usefulness to humanity — which is now suffering so severely at the hands of the food chemist — by providing fruit in vastly greater quantity than at present.

DISCUSSION

Sir Arthur Newsholme (Opening the Discussion).— I am glad to bear testimony to the value of Dr. Hoffman's work in collecting statistics on cancer, and in throwing valuable light on the distribution of that disease in various countries. Of course, those figures as he clearly stated, have only a relative value. They do not show the actual amount of cancer, but they do show that in certain countries, and particularly among civilized peoples, there is more cancer than among the uncivilized. I do not think we can go further than that, but I agree with Dr. Hoffman that there probably has been some increase in cancer.

I formerly did not hold this opinion — and justifiably so — when 25 years ago in conjunction with Mr. King I wrote a paper on the statistics of cancer which showed that a large proportion of the statistics then available were not trustworthy. I may mention one fact in connection with that paper because it has a bearing on cancer statistics. The crude figures for Ireland, Scotland, and England, respectively, showed that Ireland had more cancer than England in proportion to the population, but when we made the necessary corrections for age distribution and for sex distribution we found that, owing to the fact that the young people of Ireland had migrated to the other side of the Atlantic, the population of Ireland, on the average, was very much older than those of England and Scotland and when correction was made for this, the death rate from cancer in Ireland was considerably lower than in Scotland or England. I mention this in passing, as showing that in order to get trustworthy figures one necessarily has to consider age and sex distribution.

I echo Dr. Hoffman's wish that every one of us should help, wherever we are, in collecting statistics as to the incidence of cancer. It is only by such means that one can hope to get more light on the causes of the varying distribution of cancer in various countries.

Mention was made of the excessive amount of cancer of the tongue in males, and it is most striking that cancer of the tongue is ten times more fatal in England in men than in women. This must be due to some local irritation in the case of men which is absent in women. There are 3 possibilities, and each person will be likely to favor the factor in which he is not personally concerned:— (1) the factor of excessive smoking; (2) the factor of an after-result of syphilis; and (3) the taking of almost undiluted spirits. Which of the three is operative is difficult to determine, but after a few more years of Prohibition in America, we may be able to eliminate one of them.

So far as local irritation is concerned, it is also a remarkable fact that, in men, cancer of the pharynx is 5 times as common as among women. In China a similar male excess is found, and an ingenious explanation has been advanced that this is owing to the fact that the Chinese women serve their "lords and masters" first with hot rice, and eat it themselves only after their masters have been served — in other words, when it is cold. That is not an English or American custom, and we are bound to assume that there is some irritant to the pharynx which is operating more largely in men than in the women. Personally I am inclined to think that this irritant is whiskey, and, as I said, if America continues its present habits, in a few years light will be thrown on this question also.

Sir Arbuthnot Lane has brought forward a most interesting and important hypothesis — whether or not it is correct I do not venture to say. An hypothesis advanced by a surgeon of the distinction of Sir Arbuthnot Lane, who has made such epoch-making contributions to the progress of the science and the art of surgery, deserves and demands our most careful attention.

In the first place, the hypothesis will have been of value, even if incorrect, insofar as it makes people realize the undoubted mischief in various forms resulting from consumption of improper food. In the next place, the hypothesis is consistent with much of our knowledge of the subject of cancer, for we know that cancer follows prolonged and protracted local irritation. Inasmuch as cancer of the sigmoid flexure and rectum is most common, it is reasonable to suppose that chronic constipation has had a very marked effect in bringing this about. But it would be interesting to know from Sir Arbuthnot Lane why, if that be so, there is so much more intestinal cancer in the male than in the female. I do not know that constipation is more common in men than in women. The hypothesis is that cancer results from irritation occurring during intestinal stasis, but that there is also a toxic element which explains cancer of parts of the body other than the intestinal tract.

It is at that point that one may possibly have some slight doubt. The hypothesis is not unreasonable and one can only suspend judgment, realizing that by following the practice indicated by the hypothesis, undoubtedly improved national health will result. It is, however, difficult to explain why in certain communities chronic constipation associated with toxic absorption would lead to a large increase in cancer of the breast, whereas in other countries in Europe there is more cancer of the uterus than of the breast. The local variations in cancer of those two important organs are very great; and it is also significant that in childbearing women,

cancer of the uterus is more common than in single women, whereas the opposite of this holds true in cancer of the breast.

Those facts are difficult to explain. We need more knowledge, more information, and in the meantime, although one cannot say that the hypothesis which has been advanced by Sir Arbuthnot Lane is entirely correct, it is feasible, ingenious and useful, and one which, if adopted as a working hypothesis, will doubtless be a means of improving the health of the nation.

Dr. Hideyo Noguchi. — I wish to express my appreciation of the interesting exposé of Sir Arbuthnot Lane concerning the possible rôles played by the diet in the causation of cancers. Though not actually engaged in cancer research, I have been following with keen interest all modern developments of cancer researches, and I may take this occasion to call your attention to the fact that a part of Sir Arbuthnot Lane's idea has already received a concrete experimental demonstration in the hands of Yamagiwa and Ichikawa. In 1914, they showed that a cancer can be produced artificially, in rabbits, by keeping the inner surface of the ear painted with coal-tar preparation for a period of one year, or longer. The cancer thus produced is comparable in histological respects to a genuine carcinoma.

Thus it will be seen that a local irritation, with certain protoplasmic poisons, can produce a cancer in a lower animal, and I cannot see any reason why various injurious substances and local irritations due to abnormal alimentation cannot likewise produce cancers in the human body, which is undoubtedly far more susceptible to the influence of these noxious substances than average animals are.

Granting that this be the case, then we can see how it is possible to bring about these predisposing factors for human cancers through intestinal stagnation. I believe that the thesis treated by Sir Arbuthnot gives a renewed impetus for a thorough investigation into the rôles played by the factors associated with his theory of intestinal stasis.

Sir James Fowler.— I should like to join the previous speakers in thanking Sir Arbuthnot Lane for the exceedingly interesting paper which he has brought before us.

The question of the causation of cancer has long interested me, primarily because I was for a great many years Pathologist to the Middlesex Hospital, London. There was a large cancer hospital attached, and, according to the terms of the trust, the patients "remain until relieved by art or released by death." The post-mortem examinations on those cases are made in the post-mortem room of the hospital close by, and for many years I made those post-mortems.

From the mere making of post-mortem examinations, you would not learn much as to the cause of cancer — but much as to its distribution, and much as to the conditions of the various organs, and what is rare and what is common. The only persons who remain until the completion of the examination, when the intestines have been laid open on a large slate slab against the wall, are the pathologist who has to write up the description of the post-mortem examination, and his assistant, who does all that is otherwise necessary.

Now if you have remained until that stage, you see and get a knowledge of what I conceive to be the normal condition of the intestinal contents at the various levels, and I think you can see quite clearly that as those contents progress from the stomach downward to where there are sites probably leading to irritation, there cancer is very likely to be found. Also, the extreme rarity of cancer in the small intestine is possibly due to the fact that there the condition of the contents appears to be less irritating than elsewhere.

Many years ago, too many to state exactly — when I was attached to a ward, but was not in actual charge of the ward — a patient was admitted suffering from some obscure condition. Nodules appeared in the skin of the thorax and the abdomen. After a time, the patient agreed that one of these nodules should be removed for examination. This was done, and it had almost the actual structure of the small intestine, which, as I said, is an exceedingly rare site for cancer. The inference was that the primary growth was in the small intestine. It would have been still more interesting if the patient had remained in the hospital, but he would not remain.

That was at a time when bacteriology was coming into being and the possible causation of cancer by a microörganism was accepted. If you will think of that case, you will see that one or two things are necessary: — You have to conceive of a microörganism that can carry on its back, so to speak, a cell which, from a given part, lodges in another part and reproduces its kind; or the organism might be included in the cell. That case impressed me very much.

It is very difficult to over-emphasize the importance of local irritation. I always think of cancer in terms of a local policeman and a general policeman. The local policeman may be put out of action by local irritation; the general policeman may be put out of action I don't know how, but I can see that the more we know about the influence of the hormones on the metabolism of the body, the more we shall see that possibly their united function is that of the general policeman.

Cancer is uncontrolled cell activity.—When we know more of the cause of that cell activity and how, throughout the body, it is coördinated in such a way as to produce what we call health, then we may know more of the origin of cancer. I can conceive that it is possible we may discover a reaction which would show that a certain change had taken place in the body as the result of cancer, but I believe in the *local causation of cancer.* When we know the cause of cancer we shall know the cause of life, and I do not think that that will occur in my day, if it ever does occur.

Sir Thomas Oliver.— By those of us who know Sir Arbuthnot Lane it was quite expected that his introductory remarks would be racy in character, also by those of us who know his work, that he would lead up to the serious side of the problem to be dealt with, through intestinal stasis. I have not the least doubt, in my own mind, that there has been an increase in cancer, and, as this has occurred mostly in the gastro-intestinal canal, I do not doubt that food and irritation have a great deal to do with it. Sir Arbuthnot Lane made it a special point that the causes were irritation and absorption. As bearing upon this, I may say that experiments were carried out some time ago by applying, to the mucous surface of the vagina in animals, cells taken from a malignant growth, and nothing followed the application. But when irritation of the mucous membrane was previously induced before the application of these cells, then cancer developed,— so that the two things are necessary: irritation on the one hand, and absorption on the other. I should be glad if Sir Arbuthnot Lane could have carried us back to the earliest stage of cancer and pointed out what actually takes place in the normal cell taking on malignant action. We believe that it is the nucleus of the cell which is first affected, since that regulates nutrition and controls the whole life of the cell.

I am looking forward to the possibility of research helping us in this matter, and particularly as regards the artificial growth of cellular tissues apart from the body. It is now a comparatively easy matter to keep cells living and multiplying, apart from the body, not only for months but years. And since sarcomatous tissues are those which grow remarkably well, perhaps from such experiments we can look forward to assistance being obtained as to the actual starting of cells upon their malignant career. It seems to me that the origin of cancer is a nutritional thing in the first instance.

We are grateful to Sir Arbuthnot Lane for drawing attention to a subject which is of absorbing interest to people all the world over. Sir Arbuthnot alluded to what Mr. Ellis Barker had been doing. As members of the medical profession, we cannot close our eyes to the activities of other workers in this direction, even if

those other workers be not medical men. To realize this, we have only to look back upon the great work of Pasteur — he was not a medical man, but a chemist — so that in a matter of this kind we should at any rate accept help, no matter what the source from which it comes.

Sir Leonard Rogers.— He said that his 20 years of experience with over 2,000 post-mortems in Calcutta, and an analysis of as many more in the old records, confirmed Sir Arbuthnot Lane's statement that cancer of the large bowel is rare in native races, who pass unformed stools. He stated that he had been particularly struck by the extreme rarity of cancer of the large bowel in natives of India, although cancer of the cheek and of the epithelioma of the thighs, due to chewing pan with lime, and kangri burns respectively, shows that prolonged chronic irritation can produce the disease in natives. In the absence of bowel stasis, however, cancer of the colon rarely occurred in his Indian experience, said Sir Leonard Rogers, and most forms of cancer are much less frequent than in internal Europe, although this is mainly due to the lower average duration of life in his Calcutta post-mortem subjects.

The evidence which had been brought forward, during other discussions, of the importance of incorrect diet in sprue, and pellagra, etc., also indicates, Sir Leonard said, the advisibility of using whole-meal bread in the Tropics as well as in the Temperate Zone.

NOTE—An analysis made since the Jamaica Conference of the microscopical examination of 1190 tumors in Calcutta, however, shows that malignant tumors, including sarcomata and carcinomata, were as frequent as in 1000 tumors examined in the Pathological laboratories of St. Mary's Hospital, London.

Dr. Frederick L. Hoffman.— We all owe a debt of gratitude to Sir Arbuthnot Lane for his very lucid explanation of his theory of cancer causation. I have been a devoted student of Sir Arbuthnot Lane's theories for many years and on frequent occasions I have discussed with him matters bearing upon certain phases of the cancer problem. My own work has been chiefly concerned with the collection of cancer statistics and the ascertainment of the trend of the cancer death rate throughout the civilized world. In this connection I have gathered a wealth of data including cancer statistics for uncivilized regions. My investigations seem to fully support Sir Arbuthnot's Lane's contention that, broadly speaking, uncivilized man is relatively free from cancerous affections. When one has lived much in the Tropics and seen much of semi-civilized man one cannot but observe the enormous contrast in the mode of living. Uncivilized people live simply, eat only when hungry, and their wants are few. Civilized man eats

too much, eats too often, and frequently lives a thoroughly abnormal life practically from the time of his birth. The child is hardly old enough to move about when it is trained into habits which are an interference with natural functions and which are maintained as such throughout the whole of life.

We seem to realize today more clearly that the cause of cancer probably has much to do with the modern food supply. We are in duty bound to do something to stem the tide of cancer increase throughout the civilized world which has now reached its highest point in the recorded history of the disease. I know there are those who question the increase in cancer on certain statistical grounds more or less hypothetical. But every year up to the present year additional data derived from official sources and from all over the world indicate a further increase in the cancer death rate regardless of intensive efforts to bring about a cure in those affected.

I had a curious experience this morning in a tailor shop in which a negro boy spoke to me on the subject. He asked me if I knew anything about cancer and then said that his father had cancer of the lip 15 years ago and had been operated upon and cured, but that a year ago he had developed cancer of the throat and died as the result. He asked me if cancer of the lip could be cured why not cancer of the throat? His father was a heavy smoker using a pipe typical of the kind that illustrates that local irritation is a predisposing cause of cancer in conjunction with other bodily conditions which are likely to lead to cancer. At the present time we are making a cancer investigation in San Francisco where we are having some 300 people under personal observation. While the results are as yet numerically insufficient, I am able to say that in the overwhelming majority of cases a condition of intestinal stasis was present. Like considerations apply to admitted habits of excessive eating, particularly the eating of meat and sugar.

We have also ascertained a rather curious fact to which I do not believe attention has previously been called. In the case of men we found a considerable proportion exposed to fumes and smoke. I do not believe that we clearly realize that in modern city life there is an immense amount of external irritation due to the non-combustible elements of coal, gases, fumes, etc. The late Mr. Green of Edinburgh clearly established the evil effects of smoke and fumes as the result of modern heating methods in northern homes. It may be a mere coincidence but in our San Francisco investigation the fact has been brought out that a considerable proportion of the men die from cancer who had previously been exposed to smoke or gas fumes.

In my South American investigations among the natives of

Eastern Bolivia I found absolutely no case of cancer of the breast. This may be due to the fact that native women do not lace or wear corsets. They live very natural lives and have normal habits not interfered with by civilized customs. The food is simple and seldom excessive. I wish that Sir Arbuthnot Lane would supplement his observations on cancer of the breast with particular reference to intestinal stasis. I am inclined to think that it would be well to attach more importance to this phase of the cancer question.

I, of course, am fully well aware of divergent views not in agreement with those which have been advanced by Sir Arbuthnot Lane and others. The cancer problem is as yet in its initial stages as regards final conclusions upon almost any one of the important questions which demand consideration. No one is in a position to say as to the direction in which the best results can be secured. But all must insist upon absolute impartiality in their investigations and the full presentation of all the facts secured.

We are sincerely obliged to Sir Arbuthnot Lane for his very interesting paper.

Sir Arbuthnot Lane (*Closing the Discussion of His Own Paper*).—I thank you all very much for the patient way in which you have listened to me, and I thank the speakers for the very valuable suggestions they have made, from which I have obtained a great deal of information.

Sir Arthur Newsholme's remarks were of the greatest interest, since he has held important posts with the Government, dealing with the food of the nation. He asked why unmarried women get cancer of the breast and the ovary comparatively early in life, while the married women get cancer of the cervix:—

The cause of the latter is obviously traumatic, as indeed it is in the case of the unmarried woman whose breasts and ovaries degenerate rapidly in the presence of intestinal auto-intoxication. Material collects in these structures, which require the normal stimulus for their functional activity. This is shown by the stimulating action of prostatic secretion taken by the mouth. He also indicated the different reaction of red and towy-haired women as compared to that of the dark-haired women, when exposed to the toxins of stasis.

Sir Arthur Newsholme and I found, in a bakery in Jamaica, excellent whole-meal bread. We understood that there was very little demand for it, while the white variety was eaten generally. Sir Arthur pointed out that while white bread and water provide little or no nutritional value, whole-meal bread and water provide a diet sufficient for health.

SOME NOTES ON ALASTRIM

L. M. Moody, M.D.

The name *Alastrim* is derived from a Portuguese word meaning *to spread about.* Many other names, such as Amaas, Kaffir Pox and Milk Pox have in various countries been applied to what appears to be the same disease; and epidemics of it, or something similar, have been described in Australia, Trinidad, Africa, Brazil and elsewhere by numerous observers. All of the above-mentioned epidemics bear one common feature, namely, low mortality. Dr. Aragas, in his paper of 1911, stated that in the epidemic then in progress in Brazil there had been at least 250,000 cases, with a mortality of .5 to 2%.

The material for these notes was collected during the epidemic which began in this colony in the early part of 1920. The disease came either from Cuba or from one of the South American ports, and spread like wildfire throughout a population then poorly protected by vaccination. (The notes are compiled from a study of 202 cases.)

Apart from its remarkable nature, the great source of interest in this disease arises from the relationship which it may or may not have to smallpox; and throughout this paper a good deal of similarity, as well as some points of difference, will be noted between the two diseases.

Clinically speaking, the general symptomatology of the disease resembles that of smallpox, but is far milder in everything save the profusion of the rash; and so it becomes increasingly difficult to say how far the minor points of difference which appear on closer examination, are to be taken as evidence of fundamental difference. Certainly, however, I think that the term *mild* smallpox is a misnomer as applied to Alastrim, if the rash, the most obvious feature of the disease, be taken as evidence of severity. I pass around two photographs of one of the earlier cases, and you will see that it is not easy to call the disease a mild attack of anything.

The mode of onset is sudden and stormy, with headache,

backache and high temperature, and sometimes vomiting; but the backache is not very severe, and the combination of headache, backache and vomiting is certainly rare; vomiting, if it occurs, is, in my experience, not more frequent than once or twice.

Eruption

The rash appears between the 3rd and 5th day after the onset. The initial site of the eruption is chiefly the face, and next in order of frequency, the wrist and forearm. It begins as a few widely separated papules, not hard nor shotty, slightly elevated above the surface and superficially placed in the skin; then during the next 24 to 36 hours the rash rapidly increases so that the face, trunk and extremities are covered.

There are, broadly speaking, two types of lesion: in one the pocks are large and discrete, and in the other small and closely set. Sometimes a mixture of these two types occurs in the same patient. There are also atypical cases in which the lesions are few and widely scattered, and do not evolute in the ordinary way and may never even become pustular. They simply remain as hard lesions for a week or more, and then gradually involute.

A number of confluent and hæmorrhagic cases also occur. The two hæmorrhagic cases I saw occurred in pregnant women, and both were fatal.

The œdema which sometimes accompanies the development of the rash, is well illustrated by this series of photographs (which I have passed around) of the same case taken at different stages of the disease.

The course of the rash is, as a rule, rapid. It passes quickly through vesicle, pustule, and crust, and in many cases in 14 or 15 days the crusts have separated.

The resultant pitting is slight.

The distribution of the rash is heaviest on the face and extremities. It tends to avoid the circumorbital area and conjunctiva, though the edge of the eyelids was sometimes affected. The scalp and palms and soles showed the presence of pocks, even in mild cases. The parts lightly affected were the neck, abdomen and the inner side of thigh. Irritation or injury appears to favour the development of a

severe outcrop of rash,— and I pass around two photographs illustrative of this.

THE TEMPERATURE CURVE

The onset is marked by a rise of temperature which may reach 104° or 105° F., but which in most cases is in the region of 103°. It persists with slight variation for 3 or 4 days, then rapidly falls to normal as the rash appears. It then remains down, to rise secondarily when pustulation begins. In mild cases there is no secondary rise, and in the severe cases this rise appears to me to be proportional to the amount of infection of the pocks with skin organisms; thus when the pus is practically free from organisms, the rise is slight, and when the pus is much contaminated the rise is greater. After persisting for a few days, the temperature returns to normal and stays there unless complications occur.

BLOOD COUNTS

I made blood counts on a number of cases and my findings showed practically no diminution of the red cells and hæmoglobin. There appeared to be, however, a leucopenia in the early stages of the disease, rising to a leucocytosis 15,000 or more on maturation, according to the amount of secondary infection. The stained films showed the presence of an occasional myelocyte, the ratio of the other cells in the early stages being about normal.

URINE

The urine in the cases examined showed no albumen, except where readily accounted for by some other lesion of the urinary tract.

OTHER MANIFESTATIONS

Pain in the throat and dysphagia, accompanied by aphonia and cervical adenitis, were noted in a number of the cases. These symptoms were due to the presence of the eruption on the fauces, and presumably in the larynx and trachea.

BOWELS

In two cases there was profuse diarrhœa at the onset, but the majority were constipated.

Complications and Sequelæ

Broncho-pneumonia occurred in fatal cases in which there was much rash in the mouth and larynx — probably the result of aspiration of septic material.

Laryngitis and Aphonia sometimes occurred, but are not serious nor of long duration.

Conjunctivitis of a mild type sometimes develops.

Impetigo and Boils are, however, by far the commonest sequel.

The mortality in the disease in any large series of cases is low. Of 2,912 cases passing through the Isolation Hospital, up to March, 1921, there were 13 deaths, an average of 4.5 per 1,000.

Histology

The widespread nature of the eruption and the fact that it appears all over the body in such a short time, make it tolerably certain the virus is blood-borne. From a number of the cases Professor MacCullum and I removed bits of skin for histological examination. In sections of the tissue taken early in the disease, the blood vessels of the corium are surrounded by a dense mass of cells polynuclear, mononuclear and plasma, and the papillæ are œdematous, whilst changes in the epithelium appear to be only just beginning.

The epithelial changes consist of vacuolation and the accumulation of fluid and necrosis of the superficial epithelial cells. The pock arises from a coalescing of these areas of vacuolation, leaving bridges of epithelium between the roof and floor of the pustule. The epithelium forming the floor of the pock is broken, to communicate with the infiltrated corium, and the extent of this destruction of the floor epithelium determines the extent of the resultant scarring. In the majority of cases it is small.

Post-mortems were performed on a number of cases, but no lesions in any sense characteristic were found. One of the post-mortems was done on a pregnant woman admitted on the 12th day of the rash and bleeding from nose, mouth and uterus, and also into the skin. All the organs examined showed areas of hæmorrhage gross and microscopic, but the fœtus was apparently normal.

OCCURRENCE IN THE FŒTUS

The virus of Alastrim seems to find not much difficulty in passing through the placenta. Up to February, 1921, of 20 cases admitted to the Jubilee Hospital after attacks of Alastrim, 10 produced fœtuses with the marks of the disease, 2 produced infants which developed the disease a day or two after birth and the remaining 8 produced normal infants. I pass around 2 photographs to illustrate the disease in the fœtus and the newborn. In the latter case the mother had been successfully vaccinated 4 weeks before labour, and denies ever having had Alastrim. There were no scars of the disease to be seen, and her Wassermann reaction was negative.

VACCINATION AND ALASTRIM

In children there appears to be a natural tendency to a mild type of the disease, due partly to vaccination and partly to some other factor. Of 80 children taken at random, 26 showed scars of vaccination and 54 showed none. The disease was mild among 22, or 85% of the vaccinated, and among 44% of the unvaccinated; whereas in 134 adults without scars of vaccination, only 28% of the cases were mild in character. So that though the disease was more serious in incidence amongst the unvaccinated children than amongst vaccinated children, it was less serious amongst unvaccinated children than amongst unvaccinated adults.

In 72 adults with scars of vaccination, 47% were mild cases. There can be no doubt as to the value of recent successful vaccination as a protection against the disease. Professor MacCallum and I were continually exposed to infection for hours on end without contracting the disease. His vaccination was recent and my vaccination 5 years old.

The M. O. H. of Kingston and a number of M. O. H.'s throughout the Island have vaccinated hundreds of contacts, and are of the opinion that this measure is of the greatest value. It has more than once happened, in the spread of the disease throughout the Island, that where prompt and thorough isolation of cases and vaccination of contacts have been carried out, epidemics in various parishes have been quickly suppressed, but where these measures have been

lax the disease has spread and remained smouldering for a long time.

On the other hand, I have seen 5 cases in infants with scars of vaccination, 3 of the cases being in infants 2 years old; and Colonel Goddsmith and Major Loughnan have reported 3 cases occurring in recently successfully vaccinated men — 3 years, 1½ and 1 year after vaccination.

Vaccination does not seem, therefore, to afford absolute protection. The results of vaccination after Alastrim are interesting. Some observers have reported typical successful vaccination. This has not been my experience in 60 cases vaccinated within from the 15th day to the 12th week after Alastrim; 45 of these showed some kind of "take," but ran a course far from the typical course of vaccination. The incision healed, and no reaction was visible till about the 7th day — then a few vesicles appeared, increasing slowly in size until raised about 2 m.m. above the surface of the arm. This stage was reached in a fortnight after vaccination. There was practically no induration, no areola, no adenitis, no temperature; and on removal of the top of the vesicles in some of the cases, it was seen that the base was composed of exuberant granulations rising above the level of the skin. The lesions slowly scabbed up and dried without pustulation and the resulting scar was not the depressed scar of vaccination, but rather a local hypertrophy which slowly became level with the surface once more. The lesion was, therefore, more tardy, and showed neither the typical local nor the general reaction of vaccination.

It is only right to mention that I cultured the lymph and found that it gave a healthy growth of staphylococcus aureus. This may have had some bearing on the lesion produced. I pass around photographs of the kind of vaccination obtained. Now that the epidemic is 4 years old, cases which still bear the marks of the disease sometimes run the typical vaccination course. Dr. Moseley, who does a very large number of vaccinations on people going to America, told me that although the majority of his post-Alastrim cases appear to be immune, he has recently had 4 cases who gave a history of Alastrim 3 years ago, and who reacted in the normal way to vaccination.

ANIMAL EXPERIMENTS

In my hands the inoculation of rabbits was unsuccessful. I thought this might have been due to faulty technique, but Professor Noguchi tells me that he has not yet succeeded in growing the virus.

TREATMENT

I know of no specific treatment for the disease.

The question as to whether Alastrim and smallpox are the same, still remains *sub judice* until the causal organisms of both can be isolated and studied culturally and experimentally. But the points which suggest a difference between the diseases can be arranged under the following headings:—

1. *Constitutional symptoms.*— These are relatively slight throughout the course of Alastrim.
2. *The eruption.*— In Alastrim the eruption runs a rapid course, is not hard nor shotty in the early stages, is not umbilicated, save as a secondary feature about the 7th or 8th day, and does not form very thick pus, but rather a milky fluid.
3. *The mortality.*— I stated previously that in a series of nearly 3,000 cases in the Kingston Isolation Hospital, the mortality was 4.5 per 1,000. This was up to 1921. I shall now give some other figures, for what they are worth; I do not place much reliance on them, because the system of notification was faulty and a large number of the deaths were not medically certified, as a considerable number of cases occur without ever seeing a medical man.

	Rate
In 1920 — 3,039 cases notified, with 33 deaths	10.8 per 1,000
In 1921 — 8,195 cases notified, with 102 deaths	12.4 per 1,000
In 1922 — 1,339 cases notified, with *89 deaths *(of which only 29 were medically certified)	66.5 per 1,000
In 1923 — 1,804 cases notified, with *171 deaths *(of which only 92 were medically certified)	94.8 per 1,000

In the Kingston Isolation Hospital for the year 1923 there have been 18 deaths in 213 cases admitted; 6 of these have been in infants under 1 year.

The figures are not of much help, as any M. O. H. in the Island will tell you that a large number of cases occur and run their course without ever being brought to the notice of a medical man, but, as I said before, I give them as they are the only data available. In interpreting these figures, however, a knowledge of the local conditions is necessary.

4. *The vaccination reaction.*— This seems to present differences in the two diseases.

5. *The histological appearances.*— These seem different. The relationship that exists between smallpox and vaccination seems to be that smallpox, passed through a calf, becomes permanently changed into vaccinia, which continues to breed true. — May not Alastrim be smallpox passed through some other animal and modified into something which, though related to smallpox, will still continue to breed true to its own type?

DISCUSSION

Dr. Milton J. Rosenau (Opening the Discussion).— First permit me to felicitate Dr. Moody on his careful, scientific and conservative work on this disease, Alastrim. I regret that he is required to call it Alastrim. I infer from the remarks in his paper that if it were not so called he would perhaps have given a different title to his paper. I should like to go on record as believing that Alastrim is no more nor less than smallpox, and my reasons for believing so are these:—

First of all, smallpox is a disease which presents mutations and variations more than any other disease that we have to deal with. There is not only true smallpox, *variola vera*, but there is *variola inoculata*, there is varioloid, and there is cowpox, all of which without doubt belong in the smallpox family. Of course, we do not know about varicella, but perhaps when we know the etiological factor we shall find that it bears a kinship to the family group.

Smallpox, normally, presents large clinical differences. Everybody who has been in smallpox epidemics must have noticed that, and must have noticed that the difference between Alastrim and true smallpox is one of degree, rather than of kind. The death rate in smallpox epidemics varies from 37% to less than 0.5%.

The severity of the disease varies in different epidemics and also in the same epidemic. Smallpox is subject to mutations and vagaries. The clinical symptoms do not always follow the text-books. At Camp Jenner on the Texas border we had a high death rate,— over 1 in 3 died. There were some cases so mild that even the keenest clinicians would have had doubt about them had they seen them apart from the epidemic.

We all know there is no correlation between the pre-eruptive stage and the eruptive stage. A case may begin with fever, vomiting and severe back and head ache, and then after 3 days the fever is down and the patient wants to get up, and the eruption comes out in only 4, 5 or 6 papules, developing in vesicles, and disappears; when these cases come in a group of persons having smallpox we take them to be smallpox.

But it shows what a great difference in resistance — or virulence, if you will — this disease manifests in the United States. There we have a kind of smallpox in which the death rate is much less than that reported by Dr. Moody. For years during and after the Spanish war we had a death rate from smallpox less than .5% — that is, not more than 1 in 200 cases died. We have similar variation in other diseases. Yellow fever sometimes carries off 35%–37% of those attacked, and sometimes less than 5%. Scarlet fever is now very much milder than it used to be, and we seldom see the old malignant forms.

Without stressing this point too much, we are all familiar with the protean clinical phases of almost every disease we know — malignant cases and mild cases. The only difference that Dr. Moody makes that I have been able to see, between Alastrim and smallpox is that in Alastrim, (1) the symptoms are mild, (2) the eruption is more superficial, and (3) the mortality is low. These do not seem to be sufficient to give it a separate name.

Dr. Moody has very well stated that we can never settle this question, one way or the other, until we know the etiological cause, and so have criteria by which we can determine exactly what we are dealing with. However, if we are going to give a different name to every variety of clinical manifestation of disease, we shall have as many names for diseases as protozoölogists have for protozoa, and bacteriologists have for bacteria. That would be confusing and difficult.

The main thing from the standpoint of prevention is the fact that vaccination protects against Alastrim. That is very significant, because from the public-health standpoint that gives us the key for our attitude toward this disease. A number of years ago I was able to show that recently-recovered cases of true smallpox can be successfully vaccinated. In other words, smallpox does

not give the same protection against cowpox that cowpox does against smallpox. I am therefore not surprised to find that Dr. Moody has found that persons who have recovered from Alastrim can be successfully vaccinated.

Another objection to a separate name is that it serves to diminish preventive measures and is contrary to the principles and practice of preventive medicine. We have the same condition, precisely, in every other disease where quarantine comes into account. When we worked with yellow fever, mild cases were called "yellowoid." Mild cases of scarlet fever were called, not scarlatina, but "scarlatinoid." We also had "cholerine." It is the same with every other disease where the irksomeness of quarantine is a question. I should like to abolish the word Alastrim until it is proved that we are actually dealing with a disease other than smallpox.

Dr. Aldo Castellani.— I should like to add my congratulations to those of Professor Rosenau.

Is Alastrim really the same disease as smallpox, or are the two conditions different? Professor Rosenau is quite right in saying that we cannot reach a definite result and a definite conclusion until the two germs, if there are two separate germs, have been identified. Still, I think there are certain clinical features which tend to show that possibly the two conditions are not quite the same. (1) The profuse pustular eruption in Alastrim, while the general condition of the patient is good, is rather characteristic. (2) It would appear that in the pustules of Alastrim there is less tendency to umbilication. (3) After the eruption has disappeared, in Alastrim, the scarring seems to be much less marked than in true smallpox.

These are some of the clinical features which incline me to believe that the condition is somewhat different from true smallpox.

I may perhaps add that I have had a certain amount of experience with true smallpox, as I was for several years Consulting Physician to the Infectious Diseases Hospital, of Colombo (Ceylon) where smallpox is extremely common.

I should like to ask Dr. Moody whether he has ever tried in Alastrim the external applications of tincture of iodine and potassium permanganate? These applications, in my experience, to a certain extent prevent severe scarring and pitting, and this is very important in the case of women. I generally advise painting the face, as a matter of routine, with 1% solution of permanganate once or twice daily, and the arms and hands with tincture of iodine once daily.

Dr. Aristides Agramonte.— I hope you will excuse me if I plagiarize Dr. Rosenau's remarks. I wish to go on record as one

who believes that Alastrim and smallpox are the same disease. The question of identity was brought to me very forcefully in this way:

We were free from smallpox, or anything like it, in Cuba for ten years. Suddenly the necessity of importing great bodies of men for the cane-cutting season, brought into our country a considerable number of Jamaicans and Haitians, and co-existing with this condition we got the report of the existence of smallpox. Unfortunately, at that time the political and economic situation of the Island was not of the best, and sanitary conditions were not up to standard; only for this reason, I believe, Alastrim remained in the Island for about 5 years. It was there, when I took office in June, 1922.

It was then my belief that this disease — and I saw a good deal of it, particularly in the colored population — was nothing but a smallpox modified; either by vaccination or through the resistance of the individual. I devoted a good deal of attention and money to a thorough vaccination of the people, and at the end of 4 months Alastrim was absolutely stamped out, so that since that time — the winter of 1922-1923, we have had no Alastrim and no smallpox in Cuba. To me this is an evidence of the relation of Alastrim and true smallpox, and if Alastrim will not protect against cowpox, there is no doubt in my mind that cowpox does protect against Alastrim.

Dr. William H. Park.— The decision as to the identity of Alastrim and smallpox may be helped by a consideration of a type of typhus fever endemic in New York, as contrasted with the European type. In the United States, and especially in New York, we have had 2 forms of typhus fever, one endemic, and the other imported from Russia or elsewhere. The endemic variety is almost always mild, and is generally called Brill's Disease. The imported type has not been present for 30 years. Before that time, it frequently entered New York, and was very infectious and had a high mortality. Energetic measures were required to eradicate it. We thus had 2 clinical types of typhus fever, one due to a virulent virus, frequently fatal and very communicable,— the other to an attenuated virus which produced as a rule very mild cases. The endemic form has persisted. It is so mild that no serious efforts are made to eradicate it.

In the United States, we have at least 2 forms of smallpox. One is so slight that communities have to be prodded to prevent its spread. The other form is of severe or moderate intensity. Not infrequently the 2 viruses are being spread in the same community. Careful investigation will demonstrate that the very mild cases have received their infection from the mild virus cases,

while the moderately severe and malignant cases have been infected by the virulent virus cases. Vaccination immunizes equally against both viruses. Whether these 2 American viruses are different strains, or whether Alastrim and smallpox are different strains, may be difficult to determine. While this is being determined, the important fact is that the cowpox virus immunizes against all the viruses, so that in combating any one we safeguard against the others.

Dr. L. M. Moody (Closing the Discussion of His Own Paper).— I have to thank you for your courteous criticism of my paper. In regard to Professor Rosenau's remarks, the thing that impressed me about Alastrim was the enormous profusion of rash that appeared with slight constitutional symptoms. One has often seen cases literally covered from head to foot with rash, but not very sick, and if these cases had been true smallpox they would, I think, invariably have died. One of these severe cases was in a medical man, and he was in great pain, owing to the tension under the skin, but he made an uninterrupted recovery.

It is the profusion of rash, with low mortality and slight constitutional symptoms that makes me think that there must be some difference between the 2 diseases. Where mild smallpox has been described, there has usually been mild rash as well as other symptoms. I agree with Professor Rosenau when he says that, from the quarantine point of view, Alastrim should be regarded as smallpox. From seeing the disease in Jamaica in epidemic form for 4 years, I am of the opinion that if Alastrim had been regarded as smallpox it would have been stamped out long ago, because of the terror that smallpox has for the people. But since Alastrim is regarded as a mild disease they have not taken really seriously the preventive measures for protection against it.

Concerning Dr. Castellani's question as to whether I have tried tincture of iodine and permanganate of potassium — I have not.

In regard to the Chairman's remarks as to whether Alastrim may not be an endemic form of smallpox — that, I think, can be answered only when the etiology of both diseases is known.

THE TREATMENT OF LEPROSY

LEONARD ROGERS, F.R.C.P.

Preliminary Considerations.— Leprosy presents many difficulties as to estimating the effects of any given treatment, owing to differences in the types of the disease, and the very chronic and variable course it runs with sudden exacerbations, sometimes followed by temporary improvement. Moreover, in the anæsthetic variety there is a tendency for the progress of the disease to cease, and even for the infection to die out, although rarely until serious permanent crippling of the extremities has been produced through nerve destruction rendering treatment ineffective—but when ill-nourished begging lepers are cared for in an asylum, considerable improvement may ensue without drug treatment; for which reasons, short trials of drugs in a few cases have little value.

Even more difficult is the estimation whether great improvement — even amounting to disappearance of all active signs and infectivity of the disease under prolonged treatment — will prove permanent or not. The analogy with tuberculosis is here very close, for it is impossible to say whether in the tissues any living bacilli remain quiescent which may produce a relapse some years later. The spontaneous disappearance of extremely limited anæsthetic patches has also very occasionally been met with, although natural recoveries of the nodular forms rarely, if ever, occur; but such cases may sometimes develop nerve symptoms, which gradually predominate over the skin symptoms, forming mixed cases of leprosy.

In short, there is a nicely balanced struggle between the invading bacilli and the tissues of their host, liable occasionally to be turned in favour of the latter. This necessitates caution in judging of the effects of any remedy without long observation on a series of cases, but it also affords good hope of curative measures being discovered, by patient research, such as now appear to be within sight in certain soluble derivatives of chaulmoogra and other oils, before

dealing with which a brief review of other methods that have afforded great temporary improvement and a few apparent cures, will both be of interest and throw some light on the conditions favouring recovery.

Mineral Preparations.— Mercurial preparations have been recommended from the days of Pjetursson in Iceland, in 1769, to Radcliffe Crocker, in 1896, but have not recently met with favour. Arsenic was advised by Danielssen, in Norway, while atoxyl, arrhenal, salvarsan, and recently eparsono, have been advocated chiefly by French writers, with variable and uncertain results. Antimony intravenously has recently been advised by F. N. Cawston; and appears to be of some value in healing leprotic ulcers, although workers in Culion and elsewhere have not been able to confirm the original claims made for this form of medication. Cyanocuprol has been advised in both tuberculosis and leprosy by Japanese workers.

Iodine.— This has greater claims. Danielssen in 1886 used the iodide in the treatment and diagnosis of leprosy, and others have observed febrile and local reactions in nodular lesions, with the disappearance of old and the appearance of new nodules, as well as increased discharge of lepra bacilli in the nasal mucus, of diagnostic value following its use. Iodoform and europhen injections have been advised by Neisser and others, while Clegg and Hollmann obtained interesting febrile reactions after the inhalation of 15 to 30 minims of ethyl iodide; and Marchoux and Bourret in 1909 observed that during reactions following iodides large numbers of leprosy bacilli lose their acid-fastness and are destroyed. So the drug may be of value in conjunction with other remedies, although by itself it has failed to produce lasting beneficial results in leprosy. Ichthyol, guaiacol, strychnine, etc., have also had their advocates.

Local Treatment.— This has been advocated — especially by G. Unna — including destroying nodules by shaving off with a razor, applying carbolic acid, hydrochloric acid, caustic potash, the cautery, etc., but the claims of eradicating the disease in early cases by such measures have not been substantiated. Tr. iodine, carbon dioxide snow, ethyl chloride (Lie), trichloracetic acid, mineral baths,

X-rays, radium, and electric currents have all had their advocates: the multiplicity of remedies indicating that no really satisfactory one was available up to very recent times.

Serums against Leprosy. — These were prepared by Carrasquilla, in Colombia, in 1896, by injecting horses with the blood of lepers, while later others injected animals with antigens composed of the lepra bacillus containing juice of nodules — with more reason, but without success — and Dyer, in America, tried antivenomous and normal horse sera with no result.

Vaccines.— Some vaccines made from various acid-fast organisms have been extensively tried, with temporary good results in some cases. Tuberculin produces well-marked reactions in leprosy, but with large doses of Koch's original form more harm than good was done, an analysis of 14 papers up to 1892 showing that slight improvement was claimed in only one trial. But in 1896 Arnaud saw disappearance of nodules and improvement continuing for two years following a severe reaction; which once more illustrates the great benefit occasionally following violent reactions induced by very different lines of treatment. In 1904-5 Lie, of Norway, recorded post-mortem evidence to prove that reactions may be obtained with tuberculin injections in lepers who are quite free from lesions due to the tubercle bacillus; but he failed to get benefit in the case of lepers he treated with small doses of tuberculin, although in 1909 Baber reported remarkable improvement in several cases after the use of tuberculin combined with chaulmoogra oil.

Nastin.— This is essentially another non-specific vaccine made by Deycke, by dissolving a fatty substance extracted by ether from an acid-fast streptothrix in benzol chloride, the injection of which in leprosy also produces febrile and local reactions, sometimes followed by considerable improvement for a time. Very promising results were reported for a while by Deycke and others, until a four-year trial in British Guiana, initiated by the discoverer himself, and reported on by Wise and Minett in 1912, showed that general reactions with softening and absorption of the nodules occurred in only 3.5%. In the remainder, early, slight, general improvement during the first 3 months was followed

by retrogression, and the patients got steadily worse,— the conclusion from prolonged study of 244 unselected cases being that nastin produced only "a slight temporary check during the first 6 months of treatment, but otherwise the natural course of leprosy continued unchanged." Such temporary changes accounted for the improvements shown in Deycke's tables, while subsequently Minett found that injections of benzol chloride alone produced precisely the same effects as Deycke's nastin-B itself.

Vaccines from Supposed Acid-Fast Bacilli of Leprosy.— These have been made by Rost, Williams, Clegg, and others, from cultures obtained from cases of leprosy, which, however, Walker has recently shown cannot be distinguished from the smegma bacillus. So there are also non-specific, acid-fast bacilli, but their use has undoubtedly resulted in local and general reactions — as with tuberculin — followed in some cases by great improvement, only too often of a temporary nature, while harm can also result. Rutherfoord, in 20 carefully noted cases, found that the deterioration exceeded the improvement, while Clegg's bacillus gave negative results in Honolulu. The effects of this treatment, on the whole, are therefore disappointing.

Vaccines made from Excised Lepra Nodules.— Such vaccines, containing enormous numbers of lepra bacilli, have also produced some benefit, but this plan has obvious limitations, especially where the disease is not common. Nevertheless, the reactions produced by the various acid-fast bacillary vaccines may make them of some value in combination with other lines of treatment, as will appear presently.

Chaulmoogra Oil.— This is an old Indian remedy, which one writer thinks was referred to in the ancient writings of Susruta as "tuvaraka," but knowledge of it was introduced to western medicine by Mouat, in a paper in Volume 1 of "The Indian Annals of Medical Science," of 1853-4, and was made official in the Pharmacopœa of India in 1868, and in the Indian and Colonial addendum to the British Pharmacopœa in 1901. There has been a good deal of confusion regarding the origin of the oil, which was for many years erroneously described as being derived from the seeds of *Gynocardia odorata*, until in 1901 Sir David Prain showed that it came from the seeds of *Taraktogenus*

kurzii (King), growing along the banks of the rivers of Assam, Chittagong, and Burma. It has since been found that various species of *Hydnocarpus* — the most important of which are *H. wightiana* of Southern and Western India, and *H. Anthelmintica* of Siam, Indo-China, and China — all contain the same active, unsaturated, fatty acids as *Taraktogenus*, so that it will be convenient to include the oils of both these genera, but not that of *Gynocardia odorata*, under the term "chaulmoogra oil."

Much work has been done on the chemical constitution of these oils. Moss, as early as 1879, separated the lower melting-point acids under the term "gynocardic acid," while Power and Gornall, in 1904 and the following years, separated first the highest melting-point (68 C.) chaulmoogric acid, established its chemical formula, and made a number of compounds, including methyl and ethyl chaulmoograte. And in 1905 Power and Barrowcliff isolated from *H. wightiana* oil both chaulmoogric and a lower melting-point oil (60 C.) which they named hydnocarpic acid; — all of which I shall have to refer to again.

Chaulmoogra Oil Given Orally.— This method has long had a reputation in the treatment of leprosy, but has the great disadvantage of being so nauseating that few patients can take sufficient to do more than retard the progress of the disease. The best results have been obtained by Ralph Hopkins, in 15 years' patient work in Louisiana; 5% progressed and 71% died with 30% improved, of 88 advanced cases, and 17% of 82 incipient cases cured, 4% lesions disappeared, and 48% improved, 5% progressed, and 12% died. Thus results show that only in incipient cases was very material benefit obtained, but those results demonstrate that the oil had a definite value in leprosy. A Chinese method of giving the fresh Taraktogenus kurzii nuts orally, combined with hemp and another Chinese drug, has recently been reported — by E. A. O. Travers, of the Kuala Lumpur Leper Asylum in the Malay States — to have cleared up the symptoms of a certain number of cases of leprosy. The nuts are very cheap, and readily taken by women and children. Mr. Travers is now trying *Hydnocarpus wightiana* nuts at my suggestion, which Reed states keep fresh for months if dried in the seeds. They can be obtained, at

about 3 shillings for 80 pounds, from the Ernakalum Trading Company of Southern India, and are much easier to get than those of Taraktogenus. Competent botanists assure me, moreover, that the *Hydnocarpus wightiana* tree is likely to grow well in any hot, moist climate with a good rainfall,— that is, in just those climates where leprosy is so common — and I hope to be able to get the seeds of this species widely distributed before long, if the above results are confirmed by further experience.

The importance of these methods of administration is that they have led to the discovery of more efficient preparations derived from the oils,— the evolution which must now be described.

Gynocardic Acid.— This acid, consisting of the lower melting-point fatty acids of the oil, has been used orally since 1891, together with sodium and magnesium gynocardates, with apparent benefit in some cases. I administered gynocardic acid to a few lepers during the first decade of the present century, and came to the conclusion that it was much less irritating to the stomach, and more effective, than the whole oil. One European patient took up to 40 grains a day, for a year, with the result that a very extensive macular leprosy completely cleared up, although some nerve symptoms persisted. As early as 1912, I asked an important firm of manufacturing chemists whether they could make for me some soluble compound of gynocardic acid suitable for injection, but unfortunately received a reply in the negative.

Chaulmoogra Oil Given Intramuscularly.— This method appears to have first been used successfully by Tourtoules, in Egypt. He reported apparent recovery in one case after 650 injections, totalling 2,720 grams, in the course of 6 years, the period ending in 1899. Hallopeau, in Paris, reported benefit in the case of 9 lepers treated with combined oral and intramuscular administration, although Castel in 1899 recorded pulmonary embolism in 2 cases. Jeauselme, in 1911, injected a mixture of chaulmoogra oil, camphor, and guaiacol. And in 1914, Victor G. Heiser reported from the Philippines 14% of apparent cures in a small series of cases for prolonged periods by intramuscular injections of a mixture of equal parts of chaulmoogra oil,

camphorated oil, and resorcin; later Hopkins, McCoy, and Hollmann recorded successes by this method, which constitutes an important advance.

In 1911 Engel-Bey reported good results with a few lepers treated orally in Egypt, with antileprol made, at his suggestion, by separating the free acids of chaulmoogra oil and esterising them; while in 1913 H. Bayon gave this preparation both orally and intramuscularly.

Sodium Gynocardate Intramuscularly and Intravenously.— As the result of Heiser's success with chaulmoogra oil used intramuscularly, and of a personal visit from him in Calcutta in 1916, I renewed my attempts to obtain the active portion of the oil in a soluble form suitable for injection. With the help of Dr. Chuni L. Bose, Professor of Chemistry, and later with the whole-time assistance of Dr. Sudhamov Ghosh, D. Sc., Edinburgh, and with the financial assistance of the Indian Research Association, I obtained, first, sodium gynocardate, and subsequently similar compounds of the various fatty acids of chaulmoogra, cod liver, and other oils. I investigated their action in numerous cases of leprosy during the next four and a half years, with the following results:—

Intramuscularly, sodium gynocardate prepared from gynocardic acid with a melting point of 37 C., was better borne by Indian patients than the whole oil, and although it produced local pain and induration, it gave promising results. I next ascertained by animal experiment that it could safely, and practically painlessly, be injected intravenously in a 3% solution with only very temporary giddiness, a large medio-basilic vein allowing of weekly injection for upwards of a year. But when only small veins were available, as is often the case in women and children, irritation of the inner lining of the vein at the immediate site of injection might produce strictly localized obliterative phlebitis, limiting the injections — which was only partially prevented by the addition of ½% sodium citrate to the solution.

I next found that the sodium salts of chaulmoogra-oil fatty acids, with melting points of from 49 to 51 C., which contained both gynocardic and hydnocarpic acids, and which I called *gynocardate of soda A*, were more effective

in leprosy than those of the lower melting-point ones, while the salts of chaulmoogric acid itself were much less soluble and also less active. Eventually I came to the conclusion that the salts of the whole of the fatty acids of *Hydnocarpus wightiana* oil, containing more hydnocarpic and less chaulmoogric acid than the oil of *Taraktogenus karzii*, gave the best results. This oil has since been used in Calcutta by Muir, and by many other workers in the East, in making preparations for injections in leprosy, the tedious and expensive process of fractionation being unnecessary, now that these points have been established by careful investigations. This conclusion is confirmed by Prof. B. E. Reed, of the Pekin Union College, who has recently stated that hydnocarpus preparations, mainly supplied from Calcutta, have found favour in Singapore, the Malay States, Burma, and elsewhere, and he concluded that "the antiquity of the records of hydnocarpus, the continuity of its use in many countries, and its high chemical and therapeutic worth, give it a place of international importance."

Reactions with Destruction of the Lepra Bacilli due to Gynocardates and Hydnocarpates.— The subcutaneous injections of sodium gynocardate produced gradual im-
ment in leprosy cases, without the occurrence of
reactions in the affected tissues, but when I
give the preparation intravenously a remar-
ful phenomenon was observed, nearly
advanced nodular cases with enormou
bacilli in the affected tissues. This is
coloured plate I published in 1919, sl
swelling and softening of the leprosy
both ears. Microscopical examinati
tions in such cases revealed only a few
rod-shaped, acid-fast bacilli, together
acid-fast granules of disintegrated orga
ing that the inflammatory local reaction
vegetable substance had resulted in the des
the human tissues, of enormous numbers of t
organism, and opening up possibilities of
advance in the treatment of this hitherto in
ease.

Fever for a day or two always accompanied su

which might be induced by very minute doses of the drug, and very occasionally fever might persist for one or more months, together with softening of numerous nodules and a considerable degree of toxæmia resulting in prolonged debility. A number of new skin lesions may appear in the form of slightly raised red patches, just as occur naturally in the more acute cases of nodular leprosy, from time to time, in what Muir calls the reactionary phase of untreated cases; but, as few bacilli are found in reaction lesions, they may largely be due to inflammatory reactions excited in small deposits of lepra bacilli, which had not previously produced visible lesions while still quiescent.

As a rule, such reactionary lesions appearing during treatment, frequently clear up again rapidly, although occasionally some of them persist and the patient appears to be worse for a time. So it is now generally considered advisable to try to avoid the more severe reactions, as far as possible, by cautious dosage in the active second stage of the disease, although Muir finds that in the first stage of very limited lesions, as well as in the third quiescent stage, — when the reactionary phase no longer occurs naturally, owing to the establishment of tissue-resistance to the toxins of the bacillus — the treatment may safely be pushed, with beneficial effects. Considerable experience is thus necessary to make possible the best results, both as regards the natural course of the different varieties of leprosy, and also in the exhibition of the powerful remedies now available. This is doubtless the reason why some observers have failed to get good effects in their earlier attempts to use the new treatment.

Severe febrile and local reactions are, however, exceptional — steady improvement in their absence far more frequently ensuing — although careful observations in the wards of leper institutions enabled Muir to observe that slight rises of temperature, not noticed by the patient, nearly always occur in patients showing fairly extensive bacteriologically-positive lesions, indicating the destruction of a smaller number of bacilli of a beneficial nature. I was also able to demonstrate, by repeated microscopical examination of small excised portions of nodules from the ear or other affected part, that in the entire absence of any reac-

tions noticeable to the patient, a gradual breaking up and diminution of the lepra bacilli was brought about by repeated injections of these preparations, accompanied by slow absorption of the nodules, until nothing but a few acid-fast granules could be detected. There soon followed the entire disappearance of the bacilli from the tissues, as well as from the nasal mucous, the patients being rendered apparently free both from all the symptoms and from infectivity of the disease, 6 to 18 months usually being required to bring about this happy result in typical, but not extremely advanced, nodular cases.

In anæsthetic cases with nodular thickening of the ulnar nerves, I have also seen reactions consisting of temporary swelling of the nodules accompanied by severe pain, sometimes necessitating the use of morphine, but followed by subsidence and eventual great improvement of sensation in the area supplied by the affected nerve. In less advanced cases there was steady but slow, return of both sensation and muscular power, and eventual disappearance of the depigmented patches in various parts of the body. One of the earliest cases of this type, with foot drop greatly crippling him, lost all visible signs of the disease and became able to walk ten miles at a stretch.

On the other hand, when nerve trunks of the extremities have been extensively destroyed by prolonged disease, and fingers and toes have been lost, or the typical "claw hand," with wasting of nearly all the intrinsic muscles, has developed, complete restoration of function is obviously impossible, although a considerable degree of recovery of sensation and muscular power may take place when the disabilities are of recent origin. But not so in the long-standing crippled cases so frequently seen in Indian leper asylums, with permanent destruction of extensive portions of their distal nerve trunks by irremovable fibrous scar tissue. Such wrecks of humanity may remain in a stationary condition for several decades before some intercurrent disease releases them from their misery, and the disease can be prevented from reaching this incurable stage only by effective treatment at an early period.

An even more remarkable and important phenomenon I observed in a very few bad nodular cases developing most

prolonged and severe febrile reactions after even a single minute dose of sodium gynocardate — with great debility and inflammatory softening of extensive lesions,— has been a steady improvement over many months, without any further treatment, and with even complete recovery during the ensuing year. The following are examples:—

One of the worst cases of nodular leprosy I have seen — of 20 years' duration, with extreme thickening of the skin of the face and extensive ulceration of both the ears and the hands — had 3 months of fever after the minute intravenous dose of 0.2 c.c. of a 3% solution of sodium gynocardate. Then followed steady improvement without any further treatment, and, at the end of a year, only loose folds of skin remained at the site of the former facial nodules, and the ears and hands had completely healed.

In another patient, with a grog blossom-like nose, and on his body, raised, red, leprotic patches the size of the palms of the hands, after 2 months of reactionary fever following a few small doses of the same drug, with great loss of strength, no further treatment was given except sodium morrhuate orally, although he was anxious to have the injections continued. I sent him away for a change as soon as he began to pick up, and saw him again about a year after the reaction, when only slight pitting with some fibrous scarring remained at the sites of the former extensive lesions, sections of removed portions being quite free from acid-fast bacilli, complete recovery having thus taken place.

Such cases are quite exceptional, but their occurrence at least indicates that the action of chaulmoogra-oil soluble preparations cannot be explained solely by any direct destructive effect on the lepra bacilli,— a point of great theoretical importance.

Sodium Morrhuate and Sodium Soyate in Leprosy.—The destruction of the lepra bacillus after intravenous injections of gynocardates naturally led me to consider the possibility of inducing a similar change in the acid-fast bacillus of tuberculosis, and I consequently got Dr. S. Ghosh to extract the fatty acids from cod-liver oil and make a sodium salt for me, which I called *sodium morrhuate*. I found it made a clear solution, almost unirritating by both subcutaneous and intravenous injection. So I next tried it by both meth-

ods in leprosy, and soon observed that it could induce by either mode of administration febrile reactions in leprotic tissues with destruction of the lepra bacillus, followed by similar improvement and ultimate disappearance of all signs of the disease. Six months' treatment with practically painless subcutaneous injections of a 3% solution of sodium morrhuate brought about the absorption of very numerous raised, circinate red patches on all parts of the body of the patient, with disappearance of the lepra bacilli, leaving only lighter depigmented patches. It should be mentioned, however, that the patient left off treatment, against advice, at this stage and I found a slight recurrence in one spot a year later.

As the value of chaulmoogra oil had previously been attributed to the unique constitution for a fatty acid of a close carbon ring, the activity of sodium morrhuate in leprosy disproved that interesting theory, and led me to think that the proportion of unsaturated, fatty acids as a class might be the most important factor influencing the therapeutic value of oils in leprosy. To test this theory, I next selected some oils with a high iodine value, including soya-bean oil and Japanese-sardine oil. I also had similar sodium salts of their unsaturated fatty acids prepared, and found the latter to be irritating to human tissues, but the former, which I called *sodium soyate*, formed a clear and unirritating 3% solution suitable for injection, either subcutaneously or intravenously. But I had time to try it in only a few cases before I left India, in one of which an extensive red, raised, leprotic patch covering the whole of one cheek, together with smaller ones on other parts of the body, completely disappeared and the tissues became bacteriologically negative in the remarkably short period of six weeks. This was by far the most rapid improvement I ever saw in a case of that degree, although the effects were much less rapid in the other cases, and, as far as I know, this preparation has not since been tried on a sufficient scale to decide its precise value; but the few tests I made add yet another oil to the list of those furnishing active preparations against the acid-fast bacillus of leprosy.

In 1919 Dr. K. K. Chaterii, of Calcutta, applied my methods to nim oil, reporting great benefit for two lepers

treated by "margosates" thus prepared. During the last two years also, Muir has obtained active preparations, on the same lines, from linseed and olive oils. He concluded, however, that those prepared from the close-ring-formula fatty acids of chaulmoogra oil were rather more effective in leprosy than the others, while preparations from saturated fatty acids had very little effect in this disease. This largely confirms my theory, and at the same time opens up an unlimited field of research in connection with the many oils which may possibly furnish still more effective preparations, both in leprosy and possibly, also, in tuberculosis.

Results of Treatment with Gynocardates and Hydnocarpates and with Sodium Morrhuate.— In 1917 I reported 26 leprosy cases treated for 3 or more months with sodium gynocardates and hydnocarpates, with improvement in all, while 8 of the 12 treated for a year or more had lost all signs of the disease. In this report I remarked,—"Whether permanent results can be obtained, only time will reveal."

In 1919 I recorded 14 cases treated with sodium morrhuate. The following table shows the results obtained up to the time when I left India, early in 1920 — in all the cases I had treated for 3 months and over, the sodium morrhuate series being shown separately:—

	Not Improved	Slightly Improved	Greatly Improved	Lesions all Disappeared	Total Cases
Gynocardates and Hydnocarpates 3 months and over	1	9	20	21	51
Gynocardates and Hydnocarpates over 1 year	1	1	2	9	13
Sodium morrhuate 3 to 12 months	0	3	12	5	20

Thus, with the chaulmoogra oil preparations, in round numbers 40% had cleared up completely, and another 40% had so greatly improved that there was very good probability of their losing all signs of the disease with further treatment, giving 80% of good results — while of 13 cases treated for the sufficient period of a year or more, 9 — or

69% — had cleared up completely. The "sodium morrhuate cases" had been treated for shorter periods of from 3 months to one year, and of 20 cases 12 had greatly improved, and 5 had completely cleared up, the results being about equal to those treated with the gynocardates and hydnocarpates, when the duration of treatment is taken into account.

In only one very advanced nodular case of the total 71 cases had no improvement resulted, but it must be mentioned that as the cases represented all stages of leprosy, including some early ones, they were considerably more favorable than the average type met with in leper asylums.

Relapses.— These occur in some cases that leave off the treatment as soon as the lesions have disappeared, as I pointed out in 1919, and of 34 cases followed up since my report of 1917, 1 remained unimproved, 10 had further improved under continued treatment, in 5 the lesions had now disappeared, 13 remained clear of symptoms, and 5 had relapsed,— all cases of Indians who had left off the treatment prematurely, against my advice. Thus there is clear indication of the necessity of continuing injections for some months or, better, a year after the disappearance of outward signs of the disease, as was only to be expected in a chronic affection due to a highly resistant organism. Some of the relapsing cases cleared up again on resuming treatment. Further cases becoming stationary following hydnocarpate treatment, may proceed to clear up completely on using sodium morrhuate — which illustrates the advantage of having more than one effective remedy.

Disadvantages of the Intravenous Method.— The necessity of giving sodium hydnocarpate intravenously to obtain the best results is a serious disadvantage, both on account of its irritant action on the veins, leading to obliteration, and because of the time consumed as compared with that of an intramuscular injection. Further, sodium morrhuate has been found to deteriorate in solution through oxidation, while it is troublesome and expensive to put it up in capsules to avoid change. Shortly before I left India Dr. Ghosh made some ethyl hydnocarpate for me which I had not time to try to any extent. The next advance is due to American workers.

Ethyl-Ester Chaulmoogrates Given Intramuscularly. — In

1919 Dr. H. T. Hollmann and Professor Dean of Honolulu reported on the use of intramuscular injections of ethyl esters of the different fractions of the fatty acids of chaulmoogra oil, and confirmed my conclusion that the chaulmoogric-acid fraction produced little effect, but that the lower melting-point ones were more active. Those gentlemen obtained marked improvement in 17 out of 26 cases, improvement in 3, light improvement in 1, and no improvement in 3 who had been treated for 3 months or less,—results very similar to my earlier Calcutta results. Their method had the great practical advantage that the ethyl ester could be injected in a pure fluid state into the gluteal muscles without much pain, making it possible for a large number of cases to be dealt with in a comparatively short time. This convenient modification has since been very generally adopted in many parts of the world, with slight changes, Muir having introduced a very handy formula. In its latest form this consists of equal parts of ethyl hydnocarpate (prepared from *H. wightiana*) and of pure olive oil, with 4% double-distilled creosote (E.C.O. mixture), his former "E.C.C.O." having also contained camphor (which J. G. Samson and G. Limkako at Culion found to be useless, although they confirmed the value of the addition of creosote). Or, 10% thymol (E.T.O.) may be substituted for the creosote. Muir advises injection of these mixtures either beneath the leprous lesions or intragluteally, or both, in doses rising — by 0.5 c.c. at a time — from 0.5 c.c. up to a maximum of 10 c.c., once or twice a week. The next dose should be reduced if the temperature rises to 100 F. and remains up for more than 24 hours, while if any marked reaction occurs in the diseased tissue, injections should be stopped until it has completely subsided.

At my suggestion, Muir tried giving iodide of potassium orally in daily doses of from ½ grain to 20 grains, and found this addition may induce reactions after ethyl hydnocarpate, resulting in further improvement which was absent without it, and he has also used with success for the same purpose a vaccine of Kedrowsky's acid-fast bacillus. This illustrates the principle that a variety of substances which I showed in the historical review of former treatments to have produced reactions in leprosy, may be of value to supplement the action of the new methods.

Time does not permit me to go into further detail regarding the treatment of different stages of leprosy — which will be dealt with in a work on which Dr. Muir and I have been long engaged — and I must pass on to consider the results which have been obtained in other countries where the treatment has been tested, the most extensive trials of which we owe to American workers. In India I arranged, through the kindness of the Mission for Lepers, for a trial of both sodium gynocardate and sodium morrhuate, separately, in 13 leper asylums, and I asked Dr. Muir to make an independent analysis of the results. These showed, in 300 cases, 72% improved and 32% *greatly* improved, although the treatment had lasted only for from 2 to 12 months; and those treated for 6 months and over, up to a year, showed 100% improved and 52% *greatly* improved. The more promising cases were selected for treatment, while the two preparations gave almost identically the same results. Thus the principle was established that results from oils other than chaulmoogra may be effective in leprosy.

Results with Ethyl Chaulmoogrates and Hydnocarpates.— It is still too early to allow of anything like final conclusions regarding the precise value of the new treatment in leprosy, but the following extensive trials will afford some indications:— During last year a great test was begun in the Culion settlement, under Dr. H. W. Wade, who has kindly sent me a preliminary report showing that treatment was initiated in May, 1921, first in 500 cases during the next 2 months, and gradually increased to 1,500 by April, 1922, and 4,067 in the following year. A survey in September, 1923, showed improvement in 55.9%, while in 36% more the progress of the disease had been checked; 6.4% were worse; and 1.7% had died. The conclusion was that under the circumstances "it is felt that this result is far from discouraging,"—an opinion which is strengthened by the following figures showing the percentage of cases improved after different periods of treatment. These speak for themselves:—

Months of Treatment	Under 3	3–6	6–9	9–12	12–15
Percentage Improved	26%	12%	74%	81%	93%

Hawaii.— In this country still more instructive figures

are now available, on account of the much longer duration of the treatment by ethyl chaulmoogrates, at the Kahili Hospital, near Honolulu. There all newly discovered lepers are first sent for diagnosis and treatment, and the most advanced unamenable ones are eventually drafted to the Molokai settlement. From 1912 to 1918, before the introduction of the new, improved treatment, the percentage of yearly discharges on parole, as being recovered cases, was 6.5. During the first 2 fiscal years of the new treatment (ending on June 30, 1919 and 1920, respectively) 20 and 31 respectively were thus discharged; in 1920–21 there were 115 new admissions, and no less than 94 who were discharged, recovered,— but 23 relapsed. So in 1921–22 under stricter rules only 26 were paroled, the number being increased again the following year (1922–23) to 52.

During the last 3 years, when the full effects of the improved treatment were obtained, there were 310 admissions, and of these there were discharged, recovered, 172 — or 55.5% of the number admitted during that period; all of these were dismissed only after examination by a board of 3 experienced doctors; 16 died of complicating diseases, mostly from tuberculosis. During the last 4 years, 92 cases were transferred to Molokai as not yielding to treatment, a yearly average of 23.3%, or less than ¼ of the average yearly admissions. Further, of a total of 249 paroles in the 10 years 1912–21, there were 31, or 12.1%, that relapsed; some of them improved again, on further treatment.

To understand the full significance of these figures we must recall that the usual annual mortality among the advanced cases seen in leper asylums and settlements, is rarely less than 10%, and is often higher, while the recent Hawaiian admissions of the last 3 years show a diminution, each year, of about 10% as compared to the numbers of the previous year. It is not unreasonable to hope that similar progress may continue, in view of the number of cases now being "cleared up" in the early stages,— before they have had the prolonged opportunities of infecting their households, as when they hid their disease in the absence of any efficient treatment, instead of declaring it voluntarily, as so many have done recently. If such progress proves to be the case, I estimate that the total number of known Hawaiian

lepers will decline by about 45% within one decade, a decrease far more rapid than has ever been obtained in a tropical country in the absence of any effective treatment. This clearly illustrates the value of the new methods in the age-long struggle to stamp out leprosy.

The immense importance of treating leprosy in its early stages is proved by the following Honolulu figures of the percentages of recovered cases, in relation to the duration of the disease on commencing treatment.

Years of Duration	Under ½	½–1	1–2	2–3	3–4
Recovered	44%	18.5%	17%	10.5%	9%

Years of Duration	4–5	5–8	8–10	Over 10
Recovered	4%	1%	3%	0.5%

The much higher recovery rate in early cases is well shown by these figures, while in my own cases I found that 50% of cases treated within 3 years of the onset cleared up completely, but that only 25% of those of from 3 to 15 years' duration did so. It is also of great significance that in Hawaii, in former days, the "discharged as recovered" scarcely ever occurred in the nodular type, while under the new treatment just over ⅔ of those cases released on parole were of this previously incurable form. The younger age-groups also yielded the largest proportion of successes.

These results are in accordance, too, with Muir's recent statement that, "We have found, further, that most early cases lose all signs of active disease within a few months. . . . The most hopeful method of dealing with leprosy must therefore depend on early diagnosis and treatment." Dr. Travers, who is now in charge of a leper asylum in the Malay States — after long service there — has recorded his opinion that "if taken in time, the progress of the disease can be arrested, and that in a large proportion of cases leprosy can be actually cured." Muir also states, "Our experience shows that leprosy can almost always be diagnosed long before it becomes infectious; that is to say, the disease may be recognized by clinical signs long before bacteriological examinations are positive." And he rightly, in my opinion, advocates the multiplication of leprosy clinics, somewhat on the lines of tuberculosis dispensaries

in Britain, but with far brighter prospects of successfully staving off the plague.

Can Lasting Cures be Obtained?— It is now established that most early, and some more advanced, cases lose all symptoms and infectivity of leprosy under treatment, but it is still too early to say in what proportion of such cases the whole of the lepra bacilli have been destroyed, with consequent permanent cure, apart from reinfections; and the frequency with which relapses occur after apparent cure in tuberculosis by sanatorium treatment, necessitates the greatest caution in claiming permanent results in leprosy before sufficient time has elapsed to justify such a claim. Nevertheless, the outlook, even in this respect, appears to me to be far more favourable than in tuberculosis, for one of my early leprosy patients has now remained free from all signs of the disease for 8 years — except for a crippling of one hand, due to irreparable damage to an ulnar nerve — although he has had no treatment during the last 3 years. Several more had remained free from all symptoms for 5 and 6 years when I last heard from them.

In Hawaii 88% of the paroled cases have remained well for several years, and although it is advisable to continue some treatment for a year or so after apparent recovery, yet with this precaution there are now good grounds for hoping that the results will be permanent in a large proportion of the earlier cases, at any rate. Moreover, the evidence that the treatment actually leads to destruction of the lepra bacillus in the body, not only gives it a more hopeful place than the treatment of building up the resisting powers of the tissues by the sanatorium treatment of tuberculosis,— but such evidence also raises the still more important question of the possibility of applying the new line of treatment to the white man's scourge, a question which I dealt with in my Croonian Lecture published in *The Lancet* of June 29, 1924.

A NOTE ON THE CAUSES OF THE HISTORICAL REDUCTION OF LEPROSY

Arthur Newsholme, M.D.

There is still divergence of medical opinion as to the relative importance of infection, and of circumstances other than the receipt of an effective dose or doses of leprosy bacilli, in the causation of leprosy; and corresponding differences of opinion arise when an attempt is made to explain the disappearance of leprosy from some countries and its persistence in others.

These doubts are of interest, not only in their bearing on the prophylaxis of leprosy in countries in which it remains endemic, but also for the collateral light which they can throw on the right policy to be pursued in securing an increasingly rapid diminution of tuberculosis in our midst.

There are obvious points of resemblance and difference between the two diseases. In both, intimate prolonged personal contact, especially in circumstances of overcrowding and uncleanliness, is usually required for the production of disease. In both, the chief risk is in infancy and childhood; and it is likely that the difference between the two diseases, in respect of protracted incubation of infection, is less than is commonly supposed. That tuberculosis is more readily acquired than leprosy appears certain, though it is probable that a large proportion of the total population in temperate climates is infected with tuberculosis, and that in many tropical countries a large proportion is infected with leprosy, without the development of actual disease,—either because ineffective doses of the infective material have been received, or because a high proportion of the total population is relatively immune.

The fact that leprosy has disappeared from most temperate countries in historic times, is not without bearing on the possibility of a similar disappearance of tuberculosis. It is unlikely that, within the next century, the amount of pulmonary tuberculosis in urbanized communities will be so reduced as to prevent the tuberculization of the majority

of the population by subliminal doses of tubercle bacilli; but this contingency will eventually happen, if the reduction of tuberculosis progresses as at present. Are the apprehensions as to the risks associated with the creation of an "unsalted" population well based, in view of the freedom from leprosy, lasting over many centuries, which has been experienced in England and some other western countries?

The reasons for the historic disappearance of leprosy from these western countries deserve further study:—

In the light of our present knowledge, we can affirm that apart from specific infection there can be no leprosy. The prevention of exposure to infection, especially for children, and in particular the avoidance of exposure over protracted periods is the aim of preventive medicine. No satisfying evidence has been advanced to prove that inadequate food has any influence on the origin of the disease, though this may be so. Nor is there evidence, such as is abundantly forthcoming for tuberculosis, that alcoholic indulgence lowers resistance besides favouring exposure to infection in drink saloons; or that irritation of certain dusty occupations lights up disease which might otherwise remain dormant. There may be said, therefore, to be common agreement that the reduction of leprosy depends, and has depended in the past, on the reduction of infection. This, for instance, appears to be the conclusion of Prof. José Albert,* who, while not agreeing that chief importance attaches to the segregation of patients, and while maintaining that segregation alone cannot stamp out leprosy, adds that improved hygienic and sanitary conditions, by preventing contagion, are more effective. This merely shifts from the institution to the patient's home, the onus of preventing contagion and in support of this view is quoted the experience of Norway, in which segregation has never been complete.

The further consideration of the case of Norway is therefore indicated; and the object of this note is to support the contention that incomplete segregation of cases,— whether of leprosy or of tuberculosis,— may have marked influence in reducing the total incidence of the disease. In the case of Norway and probably also in other countries, like the

*Quoted in *The Lancet* Jan. 14, 1922, from *Journal of the Philippine Islands Medical Association*, 1921.

Philippines and Hawaii,* there does not appear to have been any such marked change in domiciliary conditions as can have effected the total improvement which has been experienced, though it is not improbable that notification of cases and increasing realization of the risk of infection, combined with adoption of simple precautions in domestic life, may have had a contributory influence in the decline of the disease.

That the institutional segregation — following the inauguration in Norway of compulsory notification of cases of leprosy, in 1856 — was the chief factor, is indicated by the following statement copied from my "Prevention of Tuberculosis" (1908) (p. 263).

> The history of the disappearance of Leprosy has been associated with the existence, on a very considerable scale, of leper asylums in the countries from which the disease has disappeared. In mediæval England such lazar houses were numerous, and although complete segregation of all patients was never secured, there doubtless was segregation of a large proportion of the total cases during a considerable part of their illness. There is no intrinsic difficulty in accepting it as fact that in leprosy—in which, as in tuberculosis, infection occurs chiefly after protracted contact of an intimate character,— the isolation of lepers must, if carried out to a sufficient extent, have served to bring about a steady decline and eventual disappearance of this disease. This conclusion is confirmed by the experience of Norway, which amounts to a check experiment. In that country, until far on in the 19th century, there were few or no leper asylums. During the first half of the 19th century Leprosy was increasing in Norway. Thus, the yearly average of fresh cases of leprosy ascertained and registered:
>
> in 1840–45 was 43
> in 1846–50 " 124
> in 1851–55 " 219
>
> Even allowing for the possibility of increasing accuracy of registration, it is clear there was no decline in this disease. In 1856 notification of cases by medical men became compulsory, and for all years onwards the official statistics state the total number of known cases of the disease and the number segregated in asylums.

*The experience of Hawaii is dealt with in a valuable paper by DR. F. L. HOFFMAN on "Leprosy as a National and International Problem." *Journal of Sociologic Medicine*, Vol. XVII, No. 2, April, 1916.

The following table gives the results up to the end of 1905:—

LEPROSY IN NORWAY

Period	*No. of Lepers per 100,000 of total population*		*Proportion per cent of total cases segregated*
	Total	*In asylums*	
1856–60	181	29	16.0
61–65	164	45	27.4
66–70	153	48	31.6
71–75	128	38	29.7
76–80	104	33	31.7
81–85	80	29	36.3
86–90	58	26	44.8
91–95	36	20	55.5
1896–1900	28	15	53.6
1901–1905	22	12	54.5

Since 1905, Leprosy has become increasingly rare in Norway. The belated establishment of segregation in Norway, as compared with the rest of Europe, and the course of events since then, leave little doubt as to the effectiveness of segregation of cases, even though only a proportion of the total number of cases were thus segregated. It will be noted that after the first 25 years, there began a rapid decline in the number of patients institutionally segregated, while at the same time the proportion of these to the number of total cases was greatly increased. *With an increasing amount of segregation of cases, the number of cases requiring segregation rapidly declined.*

No exact proportion between the rate of decline and the amount of segregation secured can be stated but the view that partial segregation has been chiefly responsible for the rapid disappearance of Leprosy from Norway is indicated by the following considerations:—

1st.— It is almost certain that cases badly housed and in impoverished circumstances, and therefore especially liable to cause large-dosed infection of others, would be especially chosen for segregation.

2nd.— The stoppage of spread of infection in a chronic disease like Leprosy, having a latent period of many years, cannot be compared with that of smallpox, in which the failure to discover a few cases will nullify the effect of the

segregation of the vast majority of cases in an outbreak. In Leprosy, as in tuberculosis, each effort of segregation may be expected to have an effect at least corresponding with the amount of effort, and possibly much greater, through the breaking of links of infection as illustrated in the next paragraph.

3rd.— The case of Leprosy may be considered alongside of that of malaria, which has disappeared as an endemic disease from England. Mosquitoes flourish in many parts of England; but owing to the drainage of marshy districts, their number is much smaller than in the past. Furthermore, the habits of the people have changed: they no longer live in hamlets close to the haunts of the Anopheles, but separated from them in large villages and towns. The links of infection have become less numerous, and the chain of events has been broken at an increasing number of points, until even in districts in which mosquitoes still prevail, the human plasmodial habitat is not available for the intermediate host.

The course of events in Leprosy is instructive in its bearing on the future control of this disease and of tuberculosis. It is scarcely necessary to decide between the relative merits of domiciliary and institutional prevention of infection, though the superiority of the latter is undoubted. Every attempt should be made to secure both; and now that in Leprosy there is great hope of cure of the disease, the motives for concealment of cases have in large measure disappeared, and we may reasonably anticipate through treatment at or in suitable institutions a more rapid success in the diminution of this disease in tropical countries.

TUBERCULOSIS IN THE TROPICS

JAMES K. FOWLER, M.D.

Mr. President and Members of the Conference: — I owe the kind invitation to attend this conference to the fact that I have been since 1910, when the Advisory Committee for Tropical Africa was instituted, one of its members. I have had from time to time as colleagues, Sir Patrick Manson, Sir Rubert Boyce, Sir Ronald Ross, Sir William Leishman, Sir William Simpson and Dr. Andrew Balfour, whose names are well known to you all.

One of the duties of the members of that committee, to which all matters relating to medicine and sanitation are referred, is to read the annual medical reports of the British Colonies. At first we were concerned only with those of Tropical Africa, but now, as the Colonial Advisory Medical and Sanitary Committee, we are in touch with all the Colonies.

The selection of the subject on which I was asked to address you was doubtless due to the fact that I have been for many years, in various capacities, in clinical contact with Pulmonary Tuberculosis. I cannot lay claim to any special experience of it from residence in the Tropics, but during the World War I was Consulting Physician to hospitals in France, for Indian and native troops, and I then saw much of Pulmonary Tuberculosis as affecting such inhabitants of tropical and sub-tropical countries.

Judging from the annual medical reports, I fear that we must conclude that the disease is on the increase among the native inhabitants of most of the British Colonies. Such a statement is not uncommon, whereas one to the opposite effect is unfortunately rare.

Tuberculosis may not loom very large in the curricula of schools of Tropical Medicine, but diseases refuse to be specialised and assert their right to world-wide prevalence; and to this law tuberculosis is no exception.

The features of tuberculosis, as it occurs in the Tropics, have to do, I think, more with the inhabitants, with their

past history in relation to it, and with their housing and mode of life, than with the climatic conditions which are peculiar to tropical countries.

The evidence is overwhelming that when tuberculosis is introduced into a country formerly free from it, the natives manifest a degree of resisting power much inferior to that shown by inhabitants of countries in which it has been present for countless generations. It may be well to consider for a moment the reason for this difference, as much appears to depend upon the explanation which is accepted.

Possibly an analogy may help toward a solution of the problem: —

In 1910 I was appointed Chairman of the Yellow Fever Commission (West Africa), of which several of those whose names I have just mentioned were also members. This work led me to take a special interest in that disease, and to ponder over the assumed immunity of the natives. I gradually came to see that no such absolute immunity existed, and that to speak of the natives as the "immunes" and of the Europeans as the "non-immunes," as was then and still is the practice, was to ignore obvious facts. There have been fatal cases among the natives in every epidemic in West Africa, not only in the past but also in recent times. The mortality rate among them, as compared with that obtaining among the Europeans, is no doubt nearly always much lower, and the type of the disease is as a rule milder, — but they are not immune.

Why is this? The answer given by Sir Rubert Boyce was as follows: "Those living in a country where the disease is endemic, at a very early period in their life get an attack of the disease which naturally confers a certain degree of immunity; later they may get subsequent attacks, but each successive attack is less serious; when manhood is reached, the subject is in all probability completely immune." [1]

The investigators sent out to West Africa by the Yellow Fever Commission, all of them carefully selected men, were specially instructed to search for evidence of the occurrence, among the natives, of attacks of fever which conformed to Sir Rubert Boyce's views, but no such evidence was obtained.

[1] *Brit. Med. Journ.*, Dec. 3, 1910.

It must, however, be admitted that it is a very difficult matter in West Africa to obtain trustworthy evidence as to the nature and incidence of the diseases which affect the natives.

I believe that in one form or another the view of Sir Rubert Boyce is still held, but I have some difficulty in accepting it. There is probably no disease an attack of which produces a more profound and lasting immunising effect upon the subject of it, than yellow fever; so rare indeed is a second attack that many deny its occurrence. Must we, notwithstanding this fact, believe that every native has 4 or 5 such attacks during his life, and requires them all to produce such a relative insusceptibility as we admit him to possess?

But this is not the only difficulty. If there are at all times sufficient infected Stegomyia in West Africa to insure that all the natives in childhood, youth and adult life receive doses of the virus adequate to confer upon them their relative degree of insusceptibility to yellow fever, why do the Europeans escape for such long periods that the memory of the last epidemic is often lost, and replaced by a hope that the disease has at last disappeared from among them? Is this then the only way in which a native race can obtain an immunity, either complete or partial, to a disease, or failing that, a higher degree of resisting power than the "newcomer" to the country? Yellow fever is preëminently a "newcomer's" disease; so also, I submit, is tuberculosis.

In the case of yellow fever, the white man usually goes to the disease from a country or an area in which it is unknown; he has little or no acquired resisting power and is fortunate, should he be attacked, if he escapes with his life.

In communities hitherto free from tuberculosis, it may first appear or be more marked among outlying sections of the people in contact with long-infected nations, or the native may himself introduce it on his return from such an infected country, whither he had gone either to work or to fight. However it may reach him, he is found with little or no resisting power, and if attacked his chances of recovery, or, apart from that, of maintaining a prolonged fight with the disease, are inferior to that of the man who has lived among it all his life.

You are all familiar with the figures showing a gradual increase in the percentage of positive results with the sub-

cutaneous tuberculin test, and with other tests, which indicate that as age advances the percentage increases until, in adult life, all or nearly all give a positive reaction. It has been stated thus: "Children not born of mothers in an advanced stage of tuberculosis, come into the world in most cases free from tuberculous infection. As each year advances a progressive number become infected, until at the age of puberty a total of one-half is reached. By the time he is adult, practically every individual is the bearer of a tuberculous lesion."

If we accept this view, are we to base our methods for dealing with the disease, and our treatment of the individual patient, upon the conclusions to which it inevitably points? This is not a merely academic question; it is one of vital importance to the clinician, as the following extracts show: —

> Meanwhile let us lose no time, but take all possible advantage of the scientific facts already established. Let these serve as a basis for concerted action in anti-tuberculous prophylaxis. Since every human being, under present social conditions, is exposed from an early age to bacillary infection, it is most necessary that children be kept under strict supervision, so that by means, for example, of tuberculin tests repeated every 6 months any recent contamination can be detected and its source determined.

Here again is the same view, stated with equally absolute precision:

"The future of tuberculosis-prevention lies in the deliberate exploitation of immunisation, by means of vaccinating doses of dead or attenuated bacilli." Is this the best way and the only way to obtain an A1 population? I think that before we can accept it, we must know clearly the meaning of a positive reaction to these tests, and also the significance of a "focal" reaction. Does a positive reaction imply that the disease is present, or does it merely indicate that at some time in the life of the individual he has been infected with tubercle? I propose to call it the "Phagocytic Register."

A disease and the virus of a disease are not the same thing.

Colonel Bushnell, in "A Study in the Epidemiology of Tuberculosis with special reference to Tuberculosis in the Tropics," writes as follows:

"The cutaneous tuberculin test is of value in diagnosis —

if the result is a positive reaction. It is, however, likely to be negative in the class of cases which most require elucidation." It cannot be claimed that this is very helpful. He quotes[1] Mirauer's results of the examination of 145 non-tuberculous patients, of whom 128 or 88% gave a positive reaction, and also of 53 tuberculous suspects, of whom 46 or 87% also gave, with 100% tuberculin, a positive reaction. The positive percentages with 25% tuberculin were 79 and 77, respectively.

In discussing Bandelier's[2] results in the examination of 500 sanatorium patients, Colonel Bushnell wisely remarks: "Whether all patients who react in so slight a degree are in need of sanatorium treatment, is a question that might be raised by the critical." As one of the critical, I venture to exercise that privilege.

Dr. Noel Bardswell, who has had an exceptional experience of this disease, in a paper on "The Sub-cutaneous Tuberculin Test"[3] writes as follows:

> 1. Failure to react to tuberculin does not exclude Tuberculous disease.
>
> 2.[4] In my opinion, the test is not a means whereby the existence or absence of tuberculous disease can be determined. Neither, when a tuberculous lesion is present, does the test give any information as to its activity. Lawrason Brown and Heise have arrived at substantially the same conclusion.

A "Focal" reaction is, however, quite another matter. Here there is a lesion in the lung, the existence of which possibly can be determined by physical or X-ray examination. In a work on "Pulmonary Tuberculosis,"[5] I described the effect of tuberculin on a man of high resisting-power, suffering from that form of the disease which goes with such a high resisting-power, *i.e.*, fibroid tuberculosis, and what was the result?

Four calcareous particles were expectorated, one surrounded by pigmented lung tissue; another portion of lung tissue and one cavity was formed. It is usually wise not to disturb sleeping

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[1] *Beib. z. Klinik d. Tub.*, Vol. 18; p. 51.

[2] *Ib.*, Vol. 2, p. 285.

[3] *Tubercle*, July, 1921, p. 433.

[4] "Twenty-four Years' Experience with the Subcutaneous Tuberculin Test." *The American Journal of Tuberculosis*, Vol. iv, No. 4, June 1920.

[5] Page 260.

dogs. On page 55 of the same work, I mentioned the case of a man whose life for 40 years had hung upon the precarious integrity of a fibrous capsule around a caseous mass, and *who, when the capsule gave way, was dead in twenty-eight days from acute miliary tuberculosis of the lungs.*

Now combine these 2 cases, and give the second man sufficient tuberculin to produce a "focal" reaction. What might, and what *almost certainly would have been,* the result? He would have been dead in a month.

Focal reactions in cases of Pulmonary Tuberculosis are in my opinion, not free from risk.

The almost universal prevalence of tuberculosis after a certain age has been reached, is held to be further confirmed by post-mortem statistics, those of Naëgeli being most often cited. It is obvious that without some measure of agreement as to what is to be accepted as a tuberculous lesion, the figures of different observers dealing with different nations are likely to show a wide divergence. If a pleural adhesion is regarded as of value equal to that of a puckered cicatrix near the apex of the lung, with a pigmented fibrocaseous or calcareous nodule about its centre and compensatory emphysematous changes around it, then, of 2 observers, one may absolutely reject the former lesion, *i.e.* the pleural adhesion, as trustworthy evidence, whereas both would accept the latter. Yet I have heard it contended that a pleural adhesion is evidence of previous tuberculous infection. I have observed that the only subjects above middle age who are, or may be, entirely free from pleural adhesions are the subjects of general emphysema. In such cases, on autopsy the lungs may come out of the thorax as readily as they do in the case of a child. How is this to be explained?

For years I made many post-mortems, and evidence of arrest of tuberculosis was always sought for. However, I was not "out" to find few or many such obsolete lesions but to prove that they were tuberculous lesions. It is a dangerous thing to be on the lookout for evidence in support of a theory, — if so, one is very likely to find it.

Some years ago my friend Sir John Rose Bradford, F.R.S. — who, during the whole of the World War was Consulting Physician at the Etaples Base — when preparing the Lumleian Lectures (1920) on "The Clinical Experiences of a Phy-

sician during the Campaign in France and Flanders, 1914–1919,"[1] asked me in what percentage of post-mortem examinations I should expect to find obsolete tuberculous lesions. My reply was, "In about 9%." He said, "I thought you would say 90%. It is curious that that is the exact figure obtained from an analysis of 2,121 post-mortems at Etaples."

The figures are as follows: —

ETAPLES AREA 1917–1918

		Number of Cases
I.	Number of post-mortem examinations	2,121
II.	Tuberculous lesions were found in	256
III.	Death in these 256 cases was directly due to tubercle, in	62
IV.	The total incidence of tuberculous lesions in all of the post-mortems made was 12%	...
V.	Obsolete tuberculous lesions were found in men dying from wounds, or some other accidental cause other than tuberculosis, in 9% of the total number examined	...

These figures are to me very interesting. Here we have a striking confirmation, from an absolutely independent and trustworthy source, of the accuracy of the figures obtained by myself and Dr. Sidney Martin, F.R.S., and published in 1891, which have hitherto been considered to be far too low.

By assembling the 3 independent observations, we get the following table: —

Date	Source of Material	No. of Post-Mortems	Obsolete Tuberculous Lesions in the Lungs	Percent. of Obsolete Lesions in the Lungs
1879–1886	Post-Mortem Room, Middlesex Hospital (Fowler)	1,943	177	9
1890–1891	Post-Mortem Room, Middlesex Hospital (Martin)	445	42	9.4
1917–1918	British Soldiers in France (Etaples) (Bradford)	2,121	191	(9)*

[1] *Lancet*, Vol. 2, 1920, p. 539.

*Total Incidence 12%

The incidence of, and mortality from, tuberculosis among the native and British troops in France, in 1918, is shown in the following table[1]: —

	Annual Case Incidence per 10,000 of Annual Average Strength	Annual Deaths per 10,000 of Annual Average Strength
South African Native Corps..	186	167
Cape Coloured Labour Corps.	444	88
Indian Native Labour Corps..	142	53
Chinese Native Labour Corps.	36	12
British Troops in France and Belgium.....	10	0.5

It is interesting to note that no obsolete tuberculous lesions were found on autopsy of the native troops, — a fact that is evidence of a lack of resisting power.

We are all agreed that racial and family characters of body and mind, endless in number and variety, may be transmitted from one generation to another through countless ages, from father or mother to son or daughter. The laws governing such inheritance are being slowly but surely worked out.

I account for the greater resisting-power of the natives of certain countries to yellow fever or to tuberculosis, by assuming that if all the minute details above referred to can be contained within their chromosomes, so also can a greater or lesser resisting power to disease, acquired by the contact of countless generations with that disease, be there and be transmitted. One individual may have a high or a low resisting-power to disease in general, whereas another may have a high or a low resisting-power to a special disease, and such special liability may be evidenced by certain characters of the body and of the mind.

The reason why it can be said that "Mary Jane brings all the catching diseases into our family," is that Mary Jane has a low resisting-power to disease in general, but she may be quite free from any special liability to, say, tuberculosis, notwithstanding the fact that one of her sisters presents all the features characteristic of that liability. It is the modern fashion either to deny the existence of such indications or to minimize their importance. I am not suggesting that the

[1] "Primitive Tribes and Tuberculosis," S. L. CUMMINS. *Trans. Soc. Trop. Med.* Vol. V, No. 7, June, 1912, p. 245.

disease itself is transmitted, as I have for years taught that in the case of private patients — that is, of those whose former history can be most closely investigated — if it is thought to be worth the trouble in the majority of such cases, it is possible to arrive at a fairly accurate opinion as to how, when, and where the tuberculous infection occurred.

Tuberculosis, and especially Pulmonary Tuberculosis, is a disease the clinical course of which presents such wide variations, and leads to such startling and unexpected terminations, either in death or recovery, that it requires almost a lifetime to obtain such a knowledge of it as enables one to speak with even a semblance of authority. Among those physicians who have had this experience, I have found but little divergence of view as to the existence of individuals of the type just referred to, nor have those physicians any doubt that in England it is a type which is now steadily diminishing in numbers; but as between these physicians and those who have not had this experience, there is a wide divergence of view. Some families, Nature's masterpieces — survivals, like Old Masters and the Classics, from much rubbish — are endowed with such a high degree of resisting power that they persist through many successive centuries without manifesting any inherited tendency to disease. I am acquainted with a member of such a family, from whom I learned that his ancestry has now been traced to 3 generations prior to 1300, and that in the elder branch of the family the succession from father to son has been unbroken through all those years. In this family today they think nothing of an age of 80 years and only begin to feel old at 90; at about 96 they may die, apparently out of consideration for the claims of the rising generation.

In the place where they originated and are still known, it is said that "If you want to get rid of a ....., the only way is to hit him on the head."

Do the "Immunists" wish us to believe that the individuals of this family for 700 years have been free from tuberculous disease, entirely owing to the timely arrival of immunizing doses of tubercle bacilli, and that hereditary influence has had nothing whatever to do with it?

These "Immunists" appear to me to have been impressed to such a degree by the overwhelming body of evidence

showing the importance of the role of infection in the transmission of the disease, that they are unable to realize the possibility of the operation of any other factor in connection with it.

I see no necessity to assume that Nature restricts herself to one method only, in arming her most finished product against the microbial millions, also of her fashioning, which to us are diseases, but which to themselves are species that must be maintained. I do not believe in the deliberate exploitation of immunization, by means of vaccinating doses of dead or attenuated tubercle bacilli, as a method of creating an A1 population. I should rather strive in every possible way to improve the physique of the nation and thus to increase the resisting power of the people to disease, including tuberculosis.

The fall in the death rate from pulmonary tuberculosis, in Great Britain, began before modern sanitary measures had had time to operate, and it will be accelerated in that and other countries when governments appreciate, to the full, that the provision of healthy homes for the people is a matter far transcending, in importance, any other with which they are called upon to deal.

EXTRACTS FROM THE SECOND SECTION OF THE ADDRESS ON TUBERCULOSIS IN THE TROPICS

James K. Fowler, M.D.

I now pass on to consider administrative measures for dealing with tuberculosis in the Tropics.

If one is attempting to estimate the result of a method of preventing or treating a given disease, it is obviously essential to insure that the cases dealt with are really examples of that disease . . . .

Notification

Whether or not notification of tuberculosis should be enforced must depend, in the Tropics, upon the local conditions and upon the degree of civilisation to which the people concerned have attained. It is useless if the notifications, as is too often the case, are received only a short time before the death of the patient, or after his decease.

The value of notification, apart from statistical inquiries, depends upon the use that is made of it in dealing with contacts, and in removing them from unhealthy surroundings.

After-care Committees and Local Tuberculosis Centers are valuable adjuncts in any administrative scheme. The latter name avoids the use of the word "Dispensary," which in Great Britain is regarded as a place where drugs are to be obtained.

Specific Remedies

I have never met with a case of Pulmonary Tuberculosis in which I have been able to satisfy myself that any good had resulted from the administration of any form of Tuberculin, but I have seen many cases in which any chance of recovery that the patient possessed had been destroyed by its use . . . .

Before any clinical use is made of such a remedy, or of anything of a similar nature which may be brought forward in the future, it is necessary that overwhelming evi-

dence should first be produced that it confers immunity on animals . . . .

SANATORIA

In temperate climes, Sanatoria at high altitudes present an undoubted advantage. In the Tropics the conditions at such altitudes, if they are available, may or may not be suitable for a native population. The Sanatorium should be situated on the healthiest site available, and should be the nucleus of a Settlement, as it is at Papworth Hall in Cambridgeshire. The other features of such a settlement appear in the following chart:

SCHEME FOR A TUBERCULOSIS SETTLEMENT

Sanatorium Department	Diagnosis Ward Clinical Ward Operating Theater — Visiting Surgeon X-ray Installation Clinical Laboratory Sanatorium Block Graduated Exercise and Graduated Labour
Hospital Department	Hospital Block
Industries Department	Huts Hostels Cottages Workshops (a) Training (b) Handicrafts Outdoor Industries Sale of Produce

(a) *Diagnosis Ward.* — All patients, on admission, should pass through this ward, but should remain there until the fact that they are really cases of pulmonary tuberculosis, has been settled. On leaving this ward, such patients would be transferred to the Sanatorium Block.

(b) *Clinical Ward.* — This ward should be occupied by cases requiring close observation, and by those in the earlier period following the operation of artificial pneumothorax, which will in future play an increasing role in the treatment of the disease among the industrial classes.

(c) *Operating Theater and X-ray Installation.* — These are essential, if artificial pneumothorax and the use of the thoracoscope form part of the treatment adopted.

(d) *Sanatorium Block.* — These wards are for patients going through the usual Sanatorium course, but in whom arrest of the disease has not yet been obtained.

Hospital. — This is for advanced cases and such as do not respond to Sanatorium treatment, or who break down when engaged in the Industries.

Huts and Hostels. — When the patient leaves the Sanatorium and has been through his course of training, it is no longer necessary for him to occupy a bed in an expensively equipped ward, and it costs much less to maintain a considerable number of two-bedded, open-air huts.

To be transferred from a Hut to a Hostel is a step in promotion: and a definite flow of promotion is one of the secrets of the successful working of a Settlement.

Cottages. — These are reserved for married men; and at Papworth when one becomes vacant, there are many applicants.

Workshops. — Training in Industries carried on in hygienic workshops involves, in temperate climes, less exposure to climatic conditions which may be harmful, than open-air occupations; but in the Tropics such considerations may not apply.

A Settlement, unlike a Colony within a ring fence, forms part of the community as a whole. Main roads may pass through it. Its shops are open to all. Its Industries employ such of the tuberculous as are capable of work; and many of them are, so their wages help to maintain themselves or their families; their work, if properly controlled, contributes to their health and promotes their happiness; the products of their labour are sold in the open market, and they are paid the wages customary in their particular industry, and consideration is given to restricted hours of labour and to an output less than that of a healthy man.

The open secrets of the successful management of the Industries of a Settlement are:

1. All heads of departments must be men who have themselves gone through the tuberculosis "mill."
2. There must be a prospect of promotion for all.

3. Repetition work which can be easily learned is the chief feature of the Industries, whereas a new handicraft can be acquired only by long application.
4. All the heavy work must be done by machinery.
5. Every department must be run on business lines; a Settlement is no place for amateurs.
6. The ideal head of a Settlement is a physician with a flair for organisation and business.

It will be seen that the Sanatorium is no longer the unit, — it has become merged in the Settlement.

That such a Tuberculosis Settlement is not a plague-spot, avoided by its neighbours, is shown by the following extract from a letter which I received from Dr. Varrier-Jones, the Director of Papworth Industries; and from many visits I am able to confirm his statements —

> We have experienced no local objection whatever. Indeed, our village is so much more prosperous than those in the surrounding country that our inhabitants are, I hear, looked upon with green-eyed jealousy. Wages are better than in the villages, and the conditions superior, so that instead of opposition we have readiness to co-operate in trade and other ways.

My advice to any Colony disposed to grapple seriously with the Tuberculosis Problem is to destroy its slums and to start a Tuberculosis Settlement on the lines which I have herein suggested.

Any country that rejects compulsory vaccination and retains its slums must pay for small-pox hospitals and tuberculosis settlements. The Tuberculosis problem is, to a very large extent, a housing problem in all parts of the world including the Tropics. When Lord Beaconsfield coined the phrase "Sanitas Sanitatum, omnia Sanitas," the world laughed. There is now evidence that glimmerings of the light of truth are reaching mankind. It is our business to see that that light shines with ever-increasing brightness.

ADDENDUM

After this paper had been sent as requested to America, to be printed in time for the Conference, a communication by Drs. A. Sandison and G. Basil Price, which bears an official character and deals with some of the points mentioned in my own paper, appeared in *The Lancet* of June 14th.

DIAGNOSIS

In "Problems in Tuberculosis" I drew attention to what I described as a "gigantic error in diagnosis" committed during the World War in regard to the soldiers of nearly all the armies engaged. We now learn that "In 1920 the Ministry of Pensions arranged for 100 cases, taken at random, of men pensioned for tuberculosis to be subjected to a comprehensive expert examination, and it then appeared that about one-third of these were wrongly diagnosed as tuberculosis."

In the evidence upon which I based my own conclusion, the percentage of error varied from 78.4 to 60, but I am glad to have the partial confirmation of my statement given by the official inquiry, which at any rate shows that that statement was not without some justification. To this point I shall, however, return later. The Ministry subsequently enlarged the scope of the Investigation so as to include 500 cases, an analysis of which forms the main subject of the communication. Of these cases 271 were invalided for Pulmonary Tuberculosis, and it is with these alone that I propose to deal.

ORIGINAL DIAGNOSIS

They were primarily classified thus:

Invaliding Disability Tuberculosis—	
T.B. pos. (pulm.)	37
T.B. neg. (pulm.)	206
Fibroid phthisis	28
	271

The use of the term "Fibroid Phthisis" without any reference to the meaning attached to it, at once throws grave doubts on the competence of the observers. The term was used by Sir Andrew Clark to describe what has long been recognised as perhaps the most chronic form of pulmonary tuberculosis, the pathological anatomy of which presents as its leading features, chronic cavities with dense fibrous walls, much retraction of the affected side, dense pleural adhesions of great thickness — the result of the contraction of the lung — and marked displacement of the thoracic viscera, especially the heart. All these changes require years of

illness for their production; yet in a total of 271 cases, 28 examples of this rare condition were met with, and in men in the prime of life who at no long previous date had been passed as fit for active military service! I hoped that the term "Fibroid Phthisis" had finally disappeared from use, and it is certainly odd to meet with it again in a classification which includes "Tuberculosis T.B. pos. (pulm.)." If, however, those who were responsible for the original Invaliding Disability were really referring to the form of the disease which I have described as "Fibroid Tuberculosis of the Lungs — *i.e.*, the fibroid transformation of miliary tubercle, a variety presenting pathological appearances the absolute antithesis of those of the "Fibroid Phthisis" of Sir Andrew Clark — then there was no necessity for placing them in a separate category, as they are now generally recognized as belonging to one of the forms of "Tuberculosis T.B. pos. (pulm.) or T.B. neg. (pulm.)," or shall we say of "Pulmonary Tuberculosis" pure and simple? I fear that we may some day find that Valvular Disease of the Heart has been subdivided into "V.D.H. pos. mur. and V.D.H. neg. mur."

It is also a very remarkable fact that those who were responsible for invaliding these men, should have been able to arrive at a diagnosis of Pulmonary Tuberculosis in *206 cases in which tubercle bacilli had never been found in the sputum.*

RESULTS OF THE INVESTIGATION

During the investigation, by the more careful examination of the sputum, and the use of methods the necessity for which has long been recognized, but which had probably not previously been employed in the cases under investigation, 13 of the 206 cases, but only 13, were *proved* to be examples of Pulmonary Tuberculosis. Concerning the remaining 193 cases it would be very interesting to know something more than that in 87 the diagnosis was certainly wrong. I do not suppose that any physician now living, with long experience of this disease, has ever in the whole course of his life made a positive diagnosis in as many as 193 cases in which the only absolutely trustworthy evidence of its presence has been absent. The further analysis of these 206 cases, which is contained in this paper, reveals other remarkable features. In 5 there was "active tuberculosis," but no

tubercle bacilli were found in the sputum; surely that is a very rare condition. In 101 the disease was "quiescent," tubercle bacilli being absent. How was the presence of "quiescent" disease ascertained, and what kind of evidence was accepted as justifying such a diagnosis? But the following statement is still more noteworthy, as it appears that among the 206 there were 75 cases which, as the result of the Investigation, were classified as "Bronchitis, Asthma, Fibrosis." One case is placed in the category "Fibroid pneumonia and other non-Tb conditions." In six cases (6) the finding was "Nil disability," which may possibly mean that there was nothing at all the matter with those patients; and five cases (5) were found to be suffering not from tuberculosis but from syphilis.

Of the 37 cases originally diagnosed as Pulmonary Tuberculosis, on the positive evidence afforded by the presence of tubercle bacilli in the sputum, the subsequent investigation showed that those organisms were then present in only 8 cases. In one (1) case the classification was "Tuberculosis active T.B. negative." Twenty cases (20) were still regarded as tuberculous, the disease being "quiescent," T.B. absent; seven (7) were classed as "Bronchitis Asthma fibrosis," and one (1) as "Fibroid pneumonia non Tuberculous."

Analysis

It appears therefore that *out of 271 cases originally invalided for Tuberculosis of the lungs, only 22 on subsequent examination presented unequivocal evidence of the continued presence of that condition.*

That is, 249 cases cured out of 271, and all due to Sanatorium Treatment! Who will venture to say a word against it in future? Artificial Pneumothorax can claim no share in this result— as it is not once mentioned in the paper.

There is, however, another possible explanation. In "Problems in Tuberculosis" I wrote as follows: —

> There had been a gigantic error in diagnosis. It may occur to some reader that this is ancient history, what is the use of recalling it? The answer is, *Because there is every reason to believe that the same error is still being made and on very nearly the same scale.*

I expressly refrain from stating that the finding of tubercle

bacilli in the sputum is the *only* test of the presence of pulmonary tuberculosis, but I do state that it is the only *positive proof* of the presence of that *disease*. If examination is made of 271 cases at the Brompton Hospital and the Frimley Sanatorium, taken at random, and being genuine examples of the disease in question, the number in which tubercle bacilli will be found to be absent and in which they have never been present at any time during the illness, or having once been present have since disappeared, will, I think, prove to be surprisingly small.

It would therefore seem, after all, that the figure given — viz., 75% — was an error on the side of moderation. Perhaps it should have been 98%.

Focal Reactions

We learn that "Diagnostic tuberculin is not now employed. The risk of revival of an apparently arrested or quiescent infection cannot be ignored, and the Ministry considered that such a risk was not justifiable." It is satisfactory to observe that somebody's protests have had their effect. The cases classed as "quiescent" were not therefore so diagnosed by the production of a "Focal Reaction."

Value of Certain Tests

Of the *complement-fixation* test it is stated that "At times, however, it is negative when undoubted infection is present, or is perversely positive in apparently non-tuberculous cases."

Of the *Von Pirquet skin reaction* we read, "No consistent results were obtained in relation to the complement-fixation test. Oftentimes the results were mutually contradictory. The skin reaction was absent in a number of cases diagnosed as tuberculosis active and quiescent, including several with tubercle bacilli in the sputum or discharges."

Radiographic Findings

With the following I am in complete agreement: — "A more uniform nomenclature by radiologists should be in use, particularly in the meanings they attach to the much-abused word "fibrosis."

In "Pulmonary Tuberculosis" (p. 174) I have discussed this question at length. I there state "They appear to

regard as common some pathological conditions which post-mortem experience indicates as being limited to certain easily recognised affections, and particularly *fibrosis of the lungs.*"

CONCLUSION

With the concluding sentence I am also in accord, *i.e.* —

"In the end it would appear that, apart from finding tubercle bacilli in the sputum or discharges, reliance must chiefly be placed on clinical evidence."

And the value of that depends upon the clinician!

DISCUSSION

Dr. H. C. Clark (*Opening the Discussion*). — I consider tuberculosis a very important problem in the Tropics. Tuberculosis and pneumonia have always played very important rôles in the Panama-Canal-Zone mortality records, if the incidence at autopsy can be depended upon to reflect their total rates.

The duration of the course of tuberculosis in the negro and the Latin-American laborer can be better represented by months than by years, as is so frequently the case among white people. Fatal cases show a widespread dissemination of the process outside the respiratory and alimentary tracts. In fact, nearly all of them die with a general acute or chronic miliary tuberculosis that has quickly become established after the primary lesions in the lungs. Almost none of the cases I have studied showed an arrested lesion, and this lesion is not at all uncommon in white people of the United States. Bone and joint and cutaneous types of tuberculosis are far less common among the laborers of the Canal Zone than among the population of the United States. The pulmonary type becoming rapidly disseminated is the common form of the disease among the negroes.

Any one interested in a detailed analysis of about 500 autopsy reports on this disease in Panama, can find my report in the *American Journal of Tropical Diseases and Preventive Medicine*, of December, 1915. During the last 3 years of my stay in the Canal Zone, it was made compulsory to send all tonsils and adenoids removed by the hospital, to the laboratory for study. Among other things we wanted to investigate, was the primary incidence of tuberculosis in tonsils. This is by no means a very common lesion; yet it certainly is not to be considered a very rare condition. The results of the examination, in so far as tuberculosis was concerned are as follows: —

The general incidence of tonsillar tuberculosis in 1,311 clinical

cases was 2.21%. The lesion was found in children between the ages of 2 years and 6 years. The 3rd decade contained a few. The youngest case was 19 months old.

Race incidence: Whites 1.45%; Blacks 3.84%; Mestizoes 4.17%.

The positive cases had associated findings as follows:

FINDINGS

	Number of Times
Phlyctenular kerato-conjunctivitis	6
Cervical lymphadenitis, tuberculous	3
Otitis media, chronic	3
Tuberculous broncho-pneumonia	1

Further details of this report can be gained through the *Proceedings of the Isthmian Canal Zone Medical Association*, for August, 1922.

Dr. William M. James. — Before I attempt to say anything on this subject I should like to express my appreciation of the points so ably brought forward by the author of this paper. To me they have been very instructive, because with us tuberculosis causes almost always 100% mortality, and so far as my own cases are concerned, which I have been able to follow from start to finish, it has caused 100% mortality. The most I have been able to do in Panama is to keep patients alive long enough to get them out of the country.

I think Sir James Fowler is quite right in bringing to this conference on tropical medicine a discussion on tuberculosis-control, because while we can control plague and malaria and yellow fever, the economic conditions that lead to bad housing and to improper nourishment are so difficult of control that I see no possibility whatever of any improvement in them for many years to come. That is why I was sorry to hear so eminent an authority state that there is very little hope in immunization. I must admit that while that is also my own point of view, I had hoped that there was some prospect of relief for these poor people. I think a plan of greatest value is the scheme which he has outlined, of a tuberculosis settlement instead of sanatoria, to protect the public and to prevent the spread of infection.

If, in a climate such as that of Panama, there is any way we can help these people I think we should adopt it, for our cases cannot follow any proper treatment for tuberculosis. There are economic reasons for this, which are absolutely beyond the control of the physician. The patient comes, usually accompanied by a member of the family, and the first instruction the clinician is given is, not

to let the patient know what is the trouble. Dr. Connor can tell you much better than I can the effects of tuberculosis on the population in the Canal Zone.

From the point of view of the clinician to whom patients come every week with every sign of incipient or advanced tuberculosis, and with a positive sputum, the clinician knowing immediately that these patients in all probability will be dead within 2 or 3 years, in spite of anything that he can do to help them, — this is one of the most distressing things occurring in practice. The patients themselves seem to look on a positive diagnosis with mingled resignation and despair, and place their trust in God rather than in any treatment they can find.

Dr. Roland C. Connor. — I hesitate to go into the subject of tuberculosis, except superficially. As we encounter the disease on the Isthmus and in the Tropics, it has seemed, as Dr. James has told you, an almost hopeless task to combat it. As I view it from the standpoint of prophylaxis, and as an aid to the population in general, it has seemed to me to be mostly a matter of spending money.

On the Isthmus of Panama, in our Health Department and in our hospitals, we have so far not provided any place where Pulmonary-Tuberculosis patients can be properly treated, except in the ward; no provision has been made for the care of the tubercular convalescent whereby he can enjoy fresh air and sunshine. We have confined our hospital treatment to a Tuberculosis Ward in the Isolation Building, and it has apparently been the wish of the authorities that we keep the patient just as short a length of time as possible and avoid overcrowding, on account of limited bed space.

In the City of Panama, I have considered the problem of tuberculosis to some extent, as I have seen a great deal of the disease, in my position as Chief of the Medical Clinic of the Ancon Hospital. We formerly had a Health Officer of Panama who was very enthusiastic regarding the question of tuberculosis. He saw that the overcrowding and poor-ventilation problem in Panama was a serious one and he at once, with the authority which he had, began to have the houses ventilated, so that the people could get fresh air, by cutting windows, etc. His work went along all right until he reached the section owned by wealthy men in Panama, who had influence and who had a good deal to say about his work. All at once this work promptly ceased. He was transferred to a local regiment for duty, and was immediately supplanted by another medical officer, who dropped the program — and the conditions are the same now in the old houses as they were formerly. The

new houses, however, are being constructed on better plans. It has seemed to me that the heads of health departments everywhere have not done all they could in their efforts to control this disease, but probably owing to a lack of money.

It is well known by physicians who have lived in the Tropics that the inclination of the negroes and the mixed breeds, Spanish and Indians, is to close up at night, shutting all the doors and windows, so that if possible they will prevent any night air from entering, — and tuberculosis will remain a serious problem until such obstacles are overcome. These conditions can be remedied by proper housing, etc.

The only thing we can do at present is, as Dr. James says, to send the patients who are able to go, to a sanitorium in the western part of the United States where we do get good results. In advanced stages all we can hope to do, is to prolong their lives until they can make the trip to the States; under proper treatment there, they often live a good many years. I advise all patients to reside permanently in the same climate, or as nearly the same, as that in which they experienced the arrest of their disease.

Sir Thomas Oliver. — We have always had considerable doubt as to the value of statistics, and I do not think that our doubts have been lightened this afternoon by the remarks Sir James Fowler has made. He has told us that in 100 post-mortem examinations made in the Middlesex Hospital, he found in the lungs indications of tubercle in only 9% of the bodies. Knowing how careful Sir James Fowler is in his investigations, his statement may be regarded as absolutely reliable. In our hospital, however, in Newcastle-upon-Tyne, the pathologists tell me, in 75% of the bodies there are signs of tubercle obsolescent or otherwise; and if my memory serves me aright, the published results of the post-mortem examinations made at the Morgue in Paris, a few years ago, showed that in at least 90% of the bodies were found illustrations of obsolescent or active tuberculosis.

It would be well if, before acceptation of these variations in statistics, there were some uniformity of opinion as to what constitutes tubercle as seen by the naked eye, — although if even this were decided upon the difficulty would not entirely disappear.

Sir James remarked that he had not obtained good results from tuberculin. I cannot go quite the full length Sir James has gone in this direction, for in several cases I have had very good, and lasting, results. One needs to be careful in the selection of patients to whom he is going to give tuberculin. In lung cases the results may not always be successful, but in patients whose glands are affected and surgical removal objected to, I have found that the

administration of tuberculin has produced good effect. I am not therefore disposed to set aside altogether the use of tuberculin in tuberculosis.

As bearing upon the question of the relationship between tuberculosis, bad housing and poor feeding, I need only remind this audience of what happened in Paris after the Franco-Prussian War. For years afterward, there was an influx of patients — mostly young people — into the hospitals, a very large proportion of whom were suffering from tuberculosis. It was the opinion of the doctors, then, that these patients were the victims of the trying conditions of life in Paris during the siege, for many of the people had to live in cellars badly ventilated and were obliged to resort to all kinds of garbage for food.

Dr. Miguel Arango. — I desire, in connection with this subject of tuberculosis, to give a few facts as regards the mortality caused by this disease in some of the large cities of Colombia, South America. There is yearly a mortality as follows:

Locality	Mortality Per 1,000 Inhabitants
Barranquilla	1.90
Bogotá	2.00
Cartagena	1.74
Santa Marta	2.30
Medellin	0.54

In the great majority of cases, the disease is found in pulmonary form; the other forms occur with less frequency.

Some time ago, I made two maps of Barranquilla. In one, I marked with red points the cases of death from tuberculosis; and in the other, I marked the various zones according to the accumulation of the inhabitants in each hectarea. Now it happened that the cases of tuberculosis and the degree of accumulation ran in a parallel course, — that is to say, the greater the accumulation of the people in a zone, the greater the number of cases of death from tuberculosis.

As regards causes of death, we have the following as the more marked: —

Alcoholism	Bad air
Syphilis	Accumulation
Uncinariasis	Carelessness
Diabetes	Dust in the street and houses
Poverty	The ordinary fly, which is abundant everywhere
Bad housing	

Dr. W. E. Deeks. — May I add a hopeful word to this discussion for those suffering from tuberculosis. It has been my experience

that the colored man is more prone to tuberculosis than the white man, and that the lesions are rarely restricted to the areas of the initial lesion, but rapidly become disseminated throughout the system. I have seen a large number of Americans who have contracted tuberculosis in the Tropics, and have invariably recommended that they go to some high, dry climate, such as New Mexico. They are advised that a properly balanced diet is essential. This should exclude fermentative foods, such as sweets and pastries and excessive amounts of starchy foods, but should include plenty of meat, eggs, milk, fresh vegetables, and fresh fruits.

In an experience extending over about 15 years I have had but one failure. In that case I did not believe the patient would live 3 months, but I had a report from him almost 5 years later. All the other patients sent to this district have recovered in from 6 months to 2 years, and have been able to return to the Tropics and resume their usual occupations. Dry, high climate appears to increase their general metabolic activities — hence the resistance to disease.

Dr. Henry Rose Carter. — I am not purposing to discuss this paper, — only to express my absolute agreement with Sir James in his repudiation of Boyce's explanation of what the latter classes as the immunity of the negro to yellow fever, *i.e.*, that this is due to repeated attacks of that disease from infancy to adult life.

In the first place, the increased resistance (I like this term better than "immunity") which the negro shows to yellow fever, is apparently less to the infection than to the effects of the infection: — less to the parasite than to its toxine. Whether negroes contract yellow fever less readily than whites may be a question, but that the case death-rate is less, and very much less, among them there is, and there can be, no question.

In the second place, this greater resistance to the toxine of the disease, as compared with that of whites, occurs in negroes independently of previous attack — *i.e.*, it is racial.

And here let me give, as St. Paul has advised, "a reason for the faith that is in us" or rather, two instances supporting it:

1. The first epidemic of yellow fever which occurred in the Brazils was in 1684. The historian of the epidemic at Bahia, of that date, da Rocha Pitta, not only notes, but *stresses*, the rarity of deaths among the blacks from this pestilence — which was fearful among the whites, — although many blacks appear to have been stricken. Naturally the negroes here, born in the country as the great majority of them were, could not have had yellow fever previously.

2. A. Corre, writing of Bazaine's expedition to Mexico, in 1864 as I recall, reports the mortality among the white troops in the *tierra caliente*, from yellow fever, as very high. In one instance, in Vera Cruz, among a company of 100 men 99 died. Yet in a brigade of, as I recall, 600 blacks from Kordofan, — furnished by the Khedive of Egypt, under the same conditions, no deaths from that disease occurred. Cornillac of Martinique and Jourdanet corroborate the last statement.

Now there has, I think, never been any report — or even a reasonable suspicion — of yellow fever in Kordofan, which is to the southward of Egypt, in eastern Africa, and what resistance these blacks had against yellow fever must have been racial, not from previous attack.

3. One more instance, and a more recent one: In 1905 there was yellow fever in some parts of the Gulf States of the United States, where none had prevailed since 1878 — 27 years before. Obviously, no negro living there all of his life, and less than 28 years old, could have had yellow fever. Yet, while there were a number of cases among this race, the deaths were very few; according to Dr. Chaissagnac, of New Orleans, among pure-bred negroes the mortality was almost negligible.

There seems no need to multiply instances of the greater resistance of the negro to the toxine of the causative organism of yellow fever. It is too well known to those who have seen this disease in both races. In the pure negro, yellow fever is, except that he propagates it, a trivial thing. To what extent, if any, he is less susceptible to attack I do not know. I am inclined to think that he is less susceptible to it, but have not data sufficient to justify a *belief* one way or the other.

Sir James Kingston Fowler (*Closing the Discussion of His Own Paper.*) — Mr. Chairman, your own remarks have been most interesting, and the method of treatment adopted in the States, and outlined by you, is very much the same as that followed by us in the treatment of our patients. It is impossible, however, to carry out this method in the treatment of the industrial classes. I think that artificial pneumothorax gives promise of relief to that class, which they never enjoyed in the past.

INFLUENZAL PNEUMONIA IN SOME OF ITS PATHOLOGICAL ASPECTS

Thomas Oliver, M.D.

I have chosen as the subject of my remarks Influenzal Pneumonia, mainly because the malady has not been confined to any particular country nor to one hemisphere; it has ravaged all parts of the civilized world, largely in consequence of international transportation.

During the last few centuries no scourge has proved more destructive to human life, than influenza. Epidemics have not only carried off hundreds of thousands of victims, after a few days' illness, but they have left as a legacy many persons the subjects of myocardial weakness or of unnameable forms of ill health whereby individuals have been robbed of their physical fitness for carrying on their life's work. A disease so widely distributed, varying in its type, and so destructive to life, appeals, therefore, to all of us and is not unworthy of the consideration of this congress.

In the city from which I come, Newcastle-upon-Tyne, there have been 5 or 6 epidemics within the last 30 years, and there, as here in Jamaica and in Central America, the attacks varied not only in character but also in their incidence as regards age periods of life. In some of the epidemics the younger people suffered the more severely; in others it was upon elderly people that the disease exercised its most malign influence. While there might be observed in one epidemic all types of the disease — pulmonary, intestinal and nervous — in another the pulmonary type predominated, and in yet another the nervous system was most affected. According to Dr. M. H. Meikle, similar events showed themselves in the Island of Jamaica. Not only did the death rates vary, but the type of the disease also varied, so that while in one area pulmonary hæmorrhage was a serious sign, in another the gastro-intestinal type of the malady prevailed; while in yet another area the striking feature was high temperature with delirium, or mental depression with apyrexia.

It is an interesting fact that no matter in which particular part of the globe the disease appeared, the malady exhibited in all places the same tendency to variation, a circumstance which enables us to discard the theory that environment plays a leading part in causing diversity of type. In many instances the march of the disease could be followed not only from country to country, but from continent to continent. When influenza appeared in Jamaica, in October, 1918, it was the prevailing opinion that the disease had entered the Island by the north coast, having been brought thither by sailors from American ports; and so rapid was the spread of the epidemic that by the following month 70,000 persons were ill, of whom 3,641 died, the chief cause of death being septic broncho-pneumonia.*

In this epidemic it was mainly the young, strong, male adults who were affected. An equally interesting fact is that after having inflicted the damage just mentioned, the disease rapidly disappeared.

On Tyneside the epidemic wrought great havoc; whole families were overcome almost simultaneously by the illness; doctors and nurses suffered, with the result that there was a considerable shortage of the usually available curative assistance. On several occasions, I visited homes wherein the parents and all, or nearly all, of the children and grown-ups were lying ill at the same time, with no member of the family physically able to render assistance to another, and occasionally with a dead body in the home. One of my colleagues was informed by a male patient that he had been one of 12 friends who had dined together one evening in a club, and that 3 weeks afterwards only 4 of the 12 men were alive.

During the first quarter of the year 1923, influenza with pneumonia, in the United States, was responsible for more than 20% of the total mortality. The epidemic appeared first in the southern states, but it gradually extended to the Atlantic Seaboard and to the Middle West cities. It was a type of influenza different from that of the world pandemic of 1918–19. There were fewer cases and fewer deaths between the ages of 20 and 45, but more in early childhood and after the age of 45. Unlike the 1918 epidemic, it did

*Annual Report Superintending Medical Officer, Jamaica.

not seriously affect the death rate from puerperal diseases, nor did the type of the disease run rapidly into pneumonia and cause death in the early stages of the illness, although it slightly swelled the general mortality rate.

During the World War influenza added considerably to the death rate of the armies of the Allies. In 1918, when the war was still in progress, the French Army lost 30,382 men, or 9.38 per 1,000 soldiers. In April, 1921, that is, 2½ years after the Armistice, influenza again carried off large numbers of young French soldiers. The epidemic appeared rather suddenly. According to Surgeon-Inspector-General Vincent, many of the men forming part of a detachment coming from Paris were attacked on the evening of their arrival at a particular garrison, with shivering, cold sweats, vomiting and severe headache, symptoms which at first suggested some form of intestinal poisoning. Of the 44 cases of pneumonia, broncho-pneumonia and pulmonary congestion which supervened, 5 of the patients succumbed rapidly to influenzal toxæmia. A few weeks afterward there came a cold snap in the weather, accompanied by snow storms, when 17,206, or 35.2 per 1,000, of the soldiers became ill, mostly the younger men, and of these 1,162 died, or 2.37 per 1,000.

Incidents such as these are appalling, owing to the rapid loss of life and the devastation of homes within a short period of time.

Just how much is to be included under the term, influenza, it is difficult to say, for the malady is probably not the result of the operation of a single microbe. While Pfeiffer's bacillus is frequently spoken of as the cause of influenza, it is clear, since the micro-organism is not found in every case, that whatever intermediary part it may play, it cannot be regarded as the sole cause of the malady. It was not believed to be the cause of the pandemic of 1918–19. Opinions are divided as to whether, when present in the expectorations, it is the primary or secondary infecting agent. As it is not always found in the early stages of the malady, it cannot therefore be the cause of the preliminary catarrh.

In a series of examinations carried out by Dr. Bernard Shaw, Assistant to the Professor of Pathology, University of Durham College of Medicine, Pfeiffer's bacillus was

found in only 1 out of 15 cases. It is an interesting fact, too, that Pfeiffer's bacillus varies in frequency in different places. That the influenzal organism, whatever its nature may be, has a special predilection for man, goes without saying, and that it is transported ærially, but especially directly from one infected person to another, is equally true.

While there are types of influenza varying from a simple cold in the head to catarrh of the bronchial tubes or to derangement of the nervous system, the disease assumes a severe character only when to it are super-added the complications caused by the presence of such other organisms as pneumococci and streptococci. Sir John W. Moore* is of the opinion that influenza, whatever its cause, predisposes to secondary infection of the lungs by diplococci and streptococci. He regards the influenza bacillus as the primary infecting agent. Whether this is so or not, the micro-organisms which cause the greatest harm are pneumococci, streptococci and micrococci catarrhales, for death is less due to influenza *qua influenza* than to secondary complications.

My main object in drawing attention to the subject of influenzal pneumonia is less to discuss the cause of influenza, the real cause of which has not yet been conclusively determined, than to demonstrate the severity of the lesions found in the lungs after death, and to show that while it is customary to speak of the cause of death as pneumonia, the pulmonary lesions usually show little resemblance to typical pneumonia. Apart from conditions present in the bronchi, the lesions in the lung are exudative and of a sero-sanguinolent nature, and they are also interstitial. On examination of microscopical sections, the striking features are the marked destruction of the mucous membrane of the bronchioles, and the disappearance of the epithelial lining, followed by softening and destruction of the bronchiolar muscular fibre. There is splenisation rather than hepatisation of the affected portions of lung; these are hæmorrhagic and œdematous, and from the open bronchioles pus escapes.

There has occurred an albuminous exudation into the bronchioles and alveoli of the lung which has broken down the limiting partitions of the latter; the exudate is for the most part non-cellular and frequently contains bubbles of air,

**Encyclopedia Medica*, Vol. 6, p. 520, 2nd Edition

some of which may be the product of chemical decomposition,— others are minute globes of residual air which are held up in the exudate, and which had never been brought into direct contact with the wall of the pulmonary capillaries. Like the epithelial lining of the mucous membrane of the bronchioles, that of the pulmonary alveoli is also destroyed. Primarily, the epithelial cells undergo hyaline degeneration with subsequent necrosis, and as the necrotizing process extends towards the alveolar wall, on the one hand, and the mucous membrane and submucosa of the bronchioles, on the other, there occurs a cellular reaction as indicated by the presence of leucocytes in large numbers. When the necrotizing process within the pulmonary alveoli extends outward, the capillaries become thrombosed; but the sero-sanguinolent exudation into the lung is not due to this incident, for since it appears before thrombosis has taken place, it is probably the result of acute congestion.

Although the lesions which I have described and which, as shown in Dr. Bernard Shaw's slides, are destructive, there are indications of organization, as revealed by disseminated areas of fibrosis. This cellular effort occurs early in the illness for within 2 to 3 weeks from the commencement of the seizure fibrosis is already well marked.

How are we to explain the lesions of the lungs in influenzal pneumonia? In health, the lining membrane of the many divisions of the respiratory tree exercises a protective influence against microbic invasion. While it is after the epithelial lining has become altered that the protective influence is lost, the question arises whether this influence is ever lost before the respiratory tract is invaded by the mouth organisms. That destruction of the epithelial lining of the respiratory tract can take place without microbic action, has been shown experimentally in animals that had inhaled poisonous gases. Destruction of the epithelial lining certainly paves the way for microbic invasion.

In influenza, apart from Pfeiffer's bacillus, there are other micro-organisms invariably present, such as pneumococci, streptococci and micrococci catarrhales. Four types of pneumococci are resident in the mouth, and these are grouped as 1, 2, 3, and 4. It is generally believed that it is Groups 1 and 2 which are the bacteriological agents present

in croupous pneumonia, and from which recovery may take place. Group 3 is the micro-organism found in fatal cases of croupous pneumonia; this organism, known as streptococcus mucosis, is, according to Flexner, broader and has a thicker capsule than the other cocci; while No. 4, also a mouth organism, is usually regarded as the influenzal pneumococcus.

The fibrotic changes which occur in the lungs call for consideration. In persons working in dusty places, and in whose lungs similar structural alterations have developed, the lesions are progressive, owing to the widely diffused particles of dust continuing to act as irritants to the walls of the pulmonary alveoli; so in the cases we have immediately in mind, while the stimulus to fibrosis may subside with the disappearance of the influenzal seizure, the structural alterations may still progress and be revealed years afterward. This has been found in children who, as a result of broncho-pneumonia following measles in early childhood, have been found at the ages of 13 and 14 to be clinically the subjects of bronchiectasis, with signs of fibrosis.

The type of fibrosis induced by the tubercle bacillus, which many of you can recall, is slowly progressive; it gives rise to a type of pulmonary phthisis consistent with considerable longevity. Similarly in many of the soldiers of the United States Army, who were drawn for the recent war from outlying country districts, and who had previously led an outdoor life, it was found that when herded together in camps these men caught measles, attended by broncho-pneumonia, and in the lungs of many of them there was distinct evidence of fibrotic changes having occurred as a result of microbic interaction. I have seen, but in a less marked form, commencing interstitial fibrosis in croupous pneumonia, where the leucocytes in the alveolar exudate had become spindle-shaped and fibrillated, and had ultimately fused themselves with the walls of the alveoli so as to inaugurate organization.

We are familiar with many of the sequelæ of influenza — the enduring nervous exhaustion and accompanying sense of fatigue, also shortness of breath on slight exertion — but it will be an interesting event to pathologists a few decades hence if they find evidence of discrete patches of fibrosis in the lungs of persons who have suffered from the influenza

of these recent years, to which the altered structure can be attributed.

In the severe types of influenza there are 2 incidents which stand out prominently, and these are the profound toxæmia, by which is probably to be explained the early delirium which develops in some patients, also the deep cyanosis with rapid heart failure, toward the relief of which medicine hitherto has been of little avail. Cyanosis developing early and rapidly, and accompanied by an increased respiratory rate, is a danger signal, and yet, in many patients, unless there is an accompanying pleurisy, there is neither complaint of pain nor a sense of urgency of breathing, although to an onlooker it would seem as if the latter were present.

From what we know of the possible events which are taking place in the lungs, there must be considerable resistance to the inhaled air passing through the viscid secretions pent up in the bronchioles; and yet, while in order to overcome this, the breathing becomes quickened and a considerable strain is placed upon the heart, the cause of the cyanosis resides rather in the respiratory centre than in the cardiac muscle, for in many of the cases the heart is not found to be dilated after death. Nor is the cause altogether in the blood, for Dr. Adolph Abrams* did not find in the blood any abnormal pigment, such as methæmoglobin.

During a patient's illness we frequently speak of the condition of his lung as that of pneumonia, but there is on physical examination, in most of the cases, none of the characteristic dullness on percussion observed in croupous pneumonia, nor the typical crepitation and tubular breathing followed later by absence of breath-sounds over the affected area; while, on the post-mortem table, it is not a well-defined solid, gray, hepatized lung which is found, but pulmonary lobes, dark red in colour, heavy œdematous and congested. The post-mortem findings are those of broncho-pneumonia with hæmorrhages and purulent bronchiolitis. It was Dr. Meikle's experience of the recent epidemic of influenza in the Island of Jamaica, that hæmoptysis was a frequent sign. The bleeding might have been due to rupture consequent upon degeneration of the walls of pulmonary vessels, as a result of the action of micro-organisms or their toxins, or, in the

*"Influenza," Edited by F. G. CROOKSHANKS, p. 327

absence of co-existing tuberculosis, the results of thrombosis and acute congestion.

It is difficult to offer an explanation of the rapid necrosis of the mucous and submucous layers of the bronchioles, with softening and disintegration of their muscular fibre, nor can we definitely state to which particular micro-organism is the actively necrotizing process to be ascribed.

The correlationship of influenza and tuberculosis deserves mention. Since a tuberculous subject is not protected against influenza, one of two immediate events may take place. He may pass safely through the attack of influenza and be apparently little the worse for it, or it may prematurely bring his life to a close; and by this I mean that, although he was the subject of pulmonary tuberculosis and of reduced vitality, yet but for the influenzal attack the probabilities were that the patient might have lived for months or years. Also in the event of modified recovery taking place, there are still two possibilities to be thought of: tuberculous lesions of the lungs which were previously quiescent may become active and run a rapid course; or, as a consequence of the local resistance of the lungs having been reduced by influenza, the individual previously healthy may be more liable to become infected by the tubercle bacillus.

DISCUSSION

Dr. Milton J. Rosenau (Opening the Discussion).— I happened to be the chairman of a commission that conducted some experiments on this disease of influenza, the commission consisting of medical officers of the United States Public Health Service, the United States Navy, in which I was then serving, and my Department of Preventive Medicine and Hygiene, at Harvard University. We focused attention on the mode of spread of the disease, being convinced that from the practical standpoint, if we had definite knowledge of the mode of spread of a disease, we should be able to control it, and that without that knowledge we should be working in the dark. We had 99 volunteers to work on, without a history of influenza, and they were all sturdy, healthy, young adults — persons serving in the Navy.

We proceeded on the supposition that Pfeiffer's bacillus was the cause of influenza, and we took old, attenuated cultures which had been in the laboratory since 1892, and placed them with

considerable trepidation upon the nostrils of these volunteers. Soon we came to the conclusion, not from these experiments alone, but from others as well, that Pfeiffer's bacillus was not the cause of influenza as the speaker has just said. We then transferred cultures, freshly isolated from the lungs of fatal cases of influenza, to the nostrils and also spread it on the throats of these volunteers, and that produced no disease. Then we took some of the material from the nose and throat, and some of the matter coughed up, and placed it in very minute quantities upon the lips and nostrils of some of our volunteers, and none of these showed any effect.

Then we took some of the raw stuff from the nose and mouth of the donors (sick with influenza, and we had literally hundreds of typical cases to choose from, this being the height of the epidemic) and we transferred that, without producing any result. It then occurred to us that perhaps we were dealing with an exceedingly frail virus that died very soon; we were collecting this from various sources, in and around Boston, and taking it to Gallups Island where we had the volunteers with nurses and attendants, and perhaps the virus could not stand that delay.

We next brought the volunteers to Chelsea and transferred the material directly from nose to nose and throat to throat without any delay, on pluggets of cotton, and none of these persons took sick in any way. After collecting a very large quantity of material, we gave some of our volunteers some of this material to drink, and filtered some of it and injected it subcutaneously, and still no one was made ill.

I shall now describe a contact experiment:— We took 20 of our volunteers and placed them in direct contact with 20 selected cases, or donors. These donors had been selected with all the care that clinical skill could make possible. We took cases as early in the disease as possible,— mild cases and severe cases — all with fever, with leucopenia, with cough and the other indications that we have of influenza. I shall follow only one case, and ask you to remember that the other 19 were doing just the same as this one:—

This volunteer is brought up to the bed beside the donor and placed on a little stool, both donor and volunteer coöperating. They shake hands and talk close together for 5 minutes. Then at a signal (ringing of a bell) these 2 persons (the donor and the volunteer) get as close together face to face as they can, and the patient breathes out quite hard while the volunteer receives this breath, breathing it in 5 times, and after that the donor coughs right into the face of the volunteer. After about 10 minutes he then moves to the next selected patient, so that each volunteer comes in contact with each of the selected cases.

This being accomplished, we took the volunteers back to the island, watched their temperature, etc., and not one of them took sick in any way. We then thought that perhaps we were not getting the donors as early in the disease as might be desirable. In fact, epidemiology points to the fact that influenza may be most communicable during its early stages — perhaps during the period of incubation. So we tried to get such cases.

The disease broke out in a naval prison at Portsmouth, New Hampshire, near Boston. We took volunteers to Portsmouth and selected 20 persons from the parts of the prison where the disease seemed to be most prevalent, in the hope that among these 20 we should find persons in some of whom the disease would later develop. No one of these prison cases did later develop the disease. Among the volunteers who received the material, nose to nose, and mouth to mouth, half of them came down with septic sore-throat. Among the prisoners we then found that the two diseases were prevalent,—i.e., influenza and septic sore-throat.

I don't want anybody to infer from these experiments that influenza is not spread by secretions from the mouth and nose, from one person to another, as we think it is, but perhaps there are factors not understood.

Dr. William H. Park.— I just wish to add a word to what Dr. Rosenau has said. We had a very interesting experience of the spread of influenza in a little mountain resort in New York State. There had been no influenza there. One of the farmers went to the city, where influenza was raging, and after a day's visit he returned to the mountain resort. He developed influenza within 2 days. Within 3 days, 2 of his children were sent home from school because of symptoms of influenza, and in 2 more days other school children came down. It was a striking example of a person's going to the city and bringing the influenza germ back to the country with him, and so starting an outbreak. The period of incubation was almost always 2 days.

As regards the question of bacteriology, of which Sir Thomas Oliver spoke, I think that the finding of the influenza bacillus is largely due to technic. In the States, during the World War, when we had a severe influenza epidemic some laboratories always found influenza bacilli, others more often streptococci, and others pneumococci, and we laughingly said, "Change the bacteriologist, and you change the bacteriological findings of the different groups." As a matter of fact, Dr. Williams, one of my associates, went to one of the laboratories where they had reported that influenza bacilli rarely appeared in the cultures, and she found that cultures from 98% of the cases showed influenza bacilli. One person trained in one technic will find in cultures from respiratory infec-

tions one type of organisms, and another trained in a different technic will find a different kind.

It is difficult to properly examine a specimen for all kinds of organisms. The Pfeiffer's influenza bacillus is present in most persons in a carrier condition. These bacilli make it very difficult to weigh its etiological importance in an outbreak of pandemic influenza. Is it a secondary or a primary infection? I approached this problem in the following way:— If the outbreak was due to a type of Pfeiffer's bacillus which, because of special virulence, was able to cause an epidemic, then cases caused by the bacillus would all show this strain and no other as the dominant organism. To make this clear, suppose a case of Type I pneumonia infected a number of persons and several of these developed pneumonia, we certainly should expect to find each of these cases infected with the Type I pneumococcus. If any one were not so infected, we should consider that the infection was obtained from another source.

I had cultures examined from a number of isolated outbreaks on small steamers, etc., and always there were found abundant Pfeiffer's bacilli. They belonged, however, in each outbreak to several different types. This, in my opinion, would be impossible if the influenza which each group of persons contracted from a single source were due to the Pfeiffer's bacillus, but it would be most natural if the unknown virus of the influenza prepared a soil for the development of the influenza bacillus which already existed in their throats or in those of their companions.

The Pfeiffer's bacillus is clearly a secondary invader.

Dr. F. L. Hoffman.— One method that might have been touched upon by Sir Thomas Oliver, as well as by Professor Rosenau, is the discovery by Brownlee that influenza epidemics run in cycles of 66 weeks, but do not develop into epidemics of serious importance unless more or less unknown meteorological factors coincide. In other words, the importance of peculiar weather conditions must not be overlooked as a direct causative factor. Unfortunately, statistically the subject demands exhaustive research, which is both costly and time-consuming. It may also be pointed out that physicians are wanting in meteorological understanding, while conversely meteorologists have no knowledge of medicine. Ordinary meteorological data are of very limited value for this purpose.

Sir Arthur Newsholme.— On the point just raised by Dr. Hoffman, I think there is something to be said in favor of the "66-weeks-internal-theory" of Dr. Brownlee, of London, but, of course, this does not account for the occurrence of the pandemics of 1891 and of 1918. How can we explain the interval between the pandemic

of 1891 and that of 1918? We are entirely ignorant as to this. The World War doubtless magnified the recent pandemic, in which more people died *than were killed by warfare*, but the war did not explain the occurrence of that pandemic.

There is another point that cannot be accounted for by epidemic, that is, that during the epidemic of 1890–91 the part of the population most seriously affected comprised the older people, 50 years of age or over, while in the pandemic of 1918 mortality fell especially among the men and women in early manhood and womanhood. I have looked carefully through the reports for a plausible explanation but have not found one, nor has Sir Thomas Oliver given us an explanation for it. We might almost suspect that the epidemic of 1891 was a different disease from that in the recent great pandemic, though I think it was the same disease in both outbreaks. However, we still have this unexplained fact.

I think we should thank Sir Thomas Oliver for bringing before us consideration of a disease over which we have hitherto had no control, in contrast to the many tropical diseases which are in process of being eliminated from the world.

Dr. Seale Harris.—Sir Thomas Oliver, in speaking of the epidemics of influenza in Europe, lays on America the blame of at least one epidemic. We are in the habit, in the United States, of laying on Europe the blame for our epidemics of influenza. I know that, as to the epidemic of 1890–91, we were of the opinion that it came from Russia; it was called Russian influenza at that time. It is true in the United States that the mortality from this epidemic was very high among old people; there were a number of senators and other distinguished men who died during that epidemic.

In the last epidemic, it is quite true that it was mostly the younger men who had influenza, and that epidemic in the United States was said to have originated in Spain; the disease is known in the United States now as "Spanish flu."

Sir Thomas spoke of the origin in the South of one epidemic of influenza. We in the South ordinarily trace our epidemics to New York; from there the infection is carried on railways to other sections of the United States. I have heard this explanation suggested of the age-periods affected by the large epidemics: that a generation arises which has not had influenza and then, when it sweeps over the country, it gets the younger generation of non-immunes. In so far as I know, there had not been an epidemic of influenza in the United States until 1890–91.

MacCollum, in the School of Hygiene of Johns Hopkins, has two cages of rats side by side. Those in one cage have lung infections of various sorts. The other rats have no lung infection of any

kind. The first rats do not get vitamine A, and the other rats do seem to get a sufficient amount of vitamine A to protect against lung infection. This may indicate some relation of nutrition to the question of immunity or susceptibility, in an epidemic of influenza.

Dr. W. E. Deeks.— I recently read of some very good results which were being obtained by Dr. Young, of Baltimore, in the treatment of septic conditions by the use of *mercurochrome* intravenously. A supply of this drug was sent to each of our hospitals, with the request that it be tried on all septic conditions which did not yield to any other specific treatment.

Among the cases which have given brilliant results by its use, are post-influenzal pneumonias. In one of these cases a blood-culture revealed the specific pneumococcus. As many of these cases remain in the hospital for weeks, and sometimes months, before resolution takes place, and as they are not infrequently followed by tuberculosis, the use of mercurochrome offers a hopeful remedy, not only in these post-influenzal pneumonias, but in a great many septic conditions such as pyelitis, puerperal septicemia, Neisser infections of the joints, and several other conditions. The reports, so far, are exceedingly favorable.

The drug is administered in a 1% solution, and 1 cc. is given for every 10 pounds of weight. The intravenous injection is usually followed by a more or less severe reaction, the temperature at times rising to 106 or 106½. Rarely, a mild form of stomatitis follows the injection,— otherwise no untoward results follow. Clinical histories of these cases will be given in our next Annual Report.

Sir Thomas Oliver (*Closing the Discussion of His Own Paper*).— I have nothing to add to what I have said. I should like to thank the speakers who have taken part in the discussion. If I had done nothing else than draw from Dr. Rosenau the account of his experiments, the short paper I have read would not have been in vain. It would be interesting to know whether, before he made his experiments upon volunteers, Dr. Rosenau had examined their blood as to the number of leucocytes contained therein.

Leucopenia in animals can be induced by the injection of benzol, and leucopenia means diminished vital resistance. A marked effect is produced on the blood and bone-marrow, and in the animals experimented upon there is occasionally found an aplastic exudate into the lungs, similar to that observed in influenza.

USE OF VACCINES AND PNEUMONIÁ ANTIBODY IN THE TREATMENT AND PREVENTION OF PNEUMONIA AND THE USE OF CONVALESCENT SERUM IN THE PREVENTION OF MEASLES

William H. Park, M.D.

Pneumonia today probably causes more deaths in the world than any other disease. In the report of the Medical Department of the United Fruit Company, for 1923, the deaths per 1,000 employes from pneumonia were 5.5, tuberculosis 2.2, malaria 1, and dysentery 1.9.

Before considering the use of serum and of vaccines in the attempt to cure and prevent pneumonia, it is necessary, in order that you may have the facts fresh in mind, to consider briefly by what means the pneumococcus invading the body causes toxic effects, and what antibodies are produced by the body in its reaction to the attack. Pneumonia is commonly divided into broncho and lobar pneumonia. The first variety is most commonly met with in the extremes of life, and as a complication of other diseases such as measles and influenza. Its bacteriology is varied. The pneumococcus is frequently the dominant organism, but more often it is associated with other bacteria such as the streptococcus and the influenza bacillus. Lobar pneumonia on the other hand is primarily a disease which attacks healthy adults, and with few exceptions the exciting organism is the pneumococcus.

This paper deals only with lobar pneumonia. The specific treatment of broncho-pneumonia is so complicated that it has as yet been hardly attempted.

How does the pneumococcus exert its harmful effects in the patient? When the pneumococcus is dissolved by the action of the bile salts or by autolysis, the resulting product is hemolytic for red-blood cells and is acutely toxic for animals. Mixed with immune serum, the toxic effects are reduced but are not completely removed. It is possible

that under favorable conditions the pneumococcus may produce a specific soluble toxin, like the streptococcus of scarlet fever. Some Dick or Dochez may discover a method to produce this toxin and its antitoxin, but up to the present time we know only of these intracellular toxins and of sera bacteriocidal, rather than antitoxic.

This is indeed a specific substance, derived from the pneumococcus which occurs not only in cultures but in the blood and urine of infected animals and man. There is as yet no evidence that this is toxic. When man or animal is given a series of injections of a killed pneumococcus culture, there is a development of antibodies. These can be detected by the agglutination or complement-fixation tests, or by the more striking protection test. A tenth of a centimeter of serum, mixed with 1,000,000 fatal doses of the culture, will protect the mouse from infection. Neufeld in 1910, noted, however, that a single serum would not be effective in protecting against all stains of pneumococci — *i.e.*, while all pneumococci have common characteristics which separate them from streptococci, they differ among themselves in the reaction to the immune bodies by different members of the group. That is, we have different types among the pneumococci. A vaccine which protects one type will give little protection against other types.

In different lands the pneumococci were studied. Through the work of Cole, Neufeld and others, it was learned that in North America and Europe, there were 3 dominant types which, in normal years, accounted for about 60 to 80% of all cases of lobar pneumonia. These were therefore named Types I, II and III. The remainder of the cases were due to other types. None of these were frequently met with. For convenience we include all the considerable number of distinct types as Type IV.

If we produced anti-pneumococci sera for each of the 3 dominant types, we would be able to treat, during ordinary seasons, ¾ of the cases with the appropriate sera. At the present time in New York City, Type No. I occurs in about 30% of the cases of lobar pneumonia, Type II in about 20%, and Type III in about 15%. The other types of pneumococci occur in about 25%; these for convenience are considered as Type IV, but really are as different among

themselves as Types I, II and III are. The remainder, 5%, are due to streptococci or other infrequently occurring bacteria. A highly potent serum of one type has a slight effect on the other type, but this is probably not enough to be of practical importance.

During the influenza outbreak, however, there was a complete reversal of the numbers due to the 3 main types and the types bunched together as Type IV. During the next 4 years, the pre-influenza conditions gradually returned; and it is safe to expect this present proportion to remain until a new epidemic of influenza-like nature occurs. In Africa, Lister discovered an additional dominant type. While the prevalence of the different types in cases of lobar pneumonia, in different parts of the world, are probably becoming similar, Lister's investigation shows that it is important that a number of cases be typed in each locality before attempting to utilize the pneumococcus vaccine or the anti-serum. For, to expect much from a vaccine or serum which does not agree with the prevalent type, would appear to be an error.

Later in this paper emphasis will be placed on the fact that an intravenous injection of the anti-pneumococcus serum will destroy any organisms in the blood, and that this is one of our strongest reasons for being hopeful of the therapeutic value of the serum. This is so important that I include a table from an article by Avery, and another table by Baldwin, showing the significance of pneumococcus septicemia. In the cases of lobar pneumonia reported by Avery and his co-workers in 1917, they found that when the blood culture was positive the case was invariably severe, and frequently fatal. The following data give their results in tabular form: —

TABLE

Type of Pneumococcus	Number of Cases Examined	Pneumococcus in Blood Cultures		Mortality	
		Pos.	Neg.	Pos.	Neg.
I.	145	34	65	36	3
II.	148	33	66	73	9
III.	55	29	71	100	28
IV.	100	21	79	52	3
Total	448	30	69	55	8

In a small series of cases just finished by Baldwin and Cecil, at Bellevue Hospital, New York, the results are very similar.

TABLE

Relation of Bacteremia and Death Rate in Pneumonia (Baldwin)

Type of Pneumococcus	Cases Studied	Cases with Positive Blood-Culture			Cases with Sterile Blood-Culture		
		Cases	Died	%	Cases	Died	%
I.	39	11	6		28	3	
II.	22	14	13		8	1	
III.	11	4	3		7	1	
IV.	35	8	7		27	2	
Total	107	37	29	78	70	7	10

These results will be referred to again when the value of this serum treatment is under consideration. Avery noted that the larger the number of colonies on the plate, the worse was the prognosis of the case from which the culture was made. Thus, 18 cases gave 1 to 30 colonies per cc. a mortality of 45%; 20 cases gave more than 30 colonies per cc. with a mortality of 100%. These results are in accord with those of others, and we can assume that the invasion of the blood by the pneumococci is a serious matter and makes the prognosis much worse.

The Use of Anti-pneumococcus Serum. — Since it is impossible to know the type of pneumococcus causing a lobar pneumonia, without making an immunological test — which may be impossible, and under the most favorable conditions requires from an hour to 12 hours' delay — it is very desirable to have a potent polyvalent serum.

This was impossible with the crude serum. Practically all horses respond to injections of the Type I pneumococcus, but only a few to Types II and III. It is practically impossible to produce a sufficiently potent serum for the 3 types in a single horse. As the dose of a potent serum is at least 50 cc., few would think it wise to give doses of 150 to 300 cc. into the vein. There is an impression that the results of serum treatment have been better in Type I cases than in those due to the other types. These two reasons have brought it about that the use of anti-pneumococci serum has been, and is still, largely confined to the use of serum for Type I cases. The serum is given intravenously,

because tests made for the blood of the treated patients show that only by this means can sufficient antibody reach the blood in sufficient concentration to produce a definite bacteriological effect.

Cole reported the first large series of Type I cases treated with potent serum. In the article by Avery, Cole and others in 1917, a mortality of 7.5% is reported for 101 cases of lobar pneumonia. This series comprised every case admitted to the hospital of the Rockefeller Institute between 1912 and 1917, with the exception that very mild cases and those evidently in convalescence were eliminated. Oliver, at the Long Island Hospital, New York, has treated with serum every Type I case for several years, and has had a mortality of 9%. The serum is administered within a few hours of admission. Cecil with the Huntoon Antibody Solution has had a similar experience.

The mortality of Type I cases without serum treatment is probably above 20%, so that we have every reason to believe that this serum has been effective. This belief is strengthened when we notice the change for the better in the patients. In a small percentage of cases there is a crisis, with an amelioration of the symptoms and the features of a natural crisis. In a large percentage of cases there is no immediate drop in temperature nor improvement in the pulse, but the patients seem to be doing better, and sooner or later recovery ensues.

The serum treatment, as administered up to the present time, has obviously many drawbacks and these have been sufficient to prevent its general use. The fact that the serum is monovalent is the greatest drawback. If only about ¼ of the cases can be benefited, while all are subjected to the annoyance of the repeated large serum-injections, and probably to later serum-sickness, it is difficult to persuade physicians to use it. This has led to attempts to discover some practical method to concentrate the antibodies and eliminate the useless substances.

Gay and Chickering have shown that the mixture of a solution of pneumococcus bodies and homologens antiserum, results in the formation of a voluminous precipitate which contains practically all the immune substances of the serum. The resulting water-clear extract possesses the

power to protect animals against pneumococcus infection. By this method a large proportion of the antibodies can be concentrated in a volume which is only 1 5 of the original serum and contains only 1/60 of the protein.

This biologic method while yielding an end-product which is ideal in many ways, is laborious in technique and the preparations obtained are of very inconsistent strength and are not stable.

The refined and concentrated serum was used to some extent at the Rockefeller Institute for Type I and Type II cases, but was in time given up. Huntoon made certain improvements in the technique, and his antibody solution has been used in over 1,000 cases. The objections to the Huntoon antibody solution are the irregualrity in strength of the different preparations, the high cost of a sufficient number of units and, most serious of all, the violent reactions which occasionally follow its intravenous injection. These objections seemed to make it inadvisable to use it in general practice. Huntoon is hopeful of so modifying the solution as to remove this occasional dangerous reaction, but it seems hardly possible that his method, any more than that of Gay and Chickering, could ever produce a potent antibody at a reasonable cost. When the injections are given subcutaneously no alarming symptoms occur; but unless enormous doses are given, no appreciable antibody appears in the blood. As previously stated, it is apparently necessary to give the pneumococcus antibody intravenously to get the desired effect.

In May of 1924, Felton, who had worked under Rosenau and was aided by a grant of money from the Influenza Commission of the Metropolitan Life Insurance Company, published a simple and efficient method for extracting the antibody from the serum. Felton discovered that when potent, freshly-drawn anti-pneumococcus serum was mixed with 10 to 20 times as much distilled water, a dense precipitate of globulin formed, which deposited at the bottom of the holding vessel. This precipitate, after further washing and antifying, was brought again into solution. The final globulin preparation had about 10 times the potency of the original serum and a much smaller amount of proteins.

Felton has successfully refined the antibody for each of

the dominant types of pneumococci, but up to the present time only Type I antibody globulin has been used in the treatment of lobar pneumonia. The tests reported by Felton show that the antibody has the same effect, in combating pneumococcus infection in animals, as the original serum. Felton believes that in addition to removing nonpotent patients' other substances by his process, he also removes something which is antagonistic to the antibody, so that the number of units in the refined serum may actually appear to be greater than the number before refining. Physicians in Boston found the use of this globulin solution was not followed by serum-rashes, but that a moderate chill frequently followed the intravenous injection.

Felton kindly refined a considerable quantity of health-department serum, and returned to me his refined preparation. I distributed it to a number of New York City hospitals. The results obtained from its use confirmed those reported by Felton. By far the largest number of patients who received the refined serum, were in Bellevue Hospital. As I personally observed many of these cases while under treatment, and as they were under the most careful medical and laboratory control, I will confine my remarks to them only. I am indebted to Dr. Cecil and Dr. Baldwin for the laboratory and clinical findings.

IDENTIFICATION OF THE ANTIBODY IN BLOOD AFTER ADMINISTRATION

A brief study of the fate of the concentrated Type I solution, when given intravenously, leads to the conclusion that following the administration of 5 to 10 cc., definite protective power is demonstrable in the serum of the patient for at least 24 hours.

The following experiments may be cited.

Case 1. — Demonstration of the Antibody in the Blood Immediately after the Injections and 24 Hours Later.

J. S., male, aged 56, with pneumococcus Type I pneumonia, received the first dose of Felton's solution, amounting to 6 cc. of Lot No. 8 on the morning of the 4th day of his illness. Before administration and immediately after, blood was taken for protective bodies and culture. Pre-

vious to administration, no protective bodies for pneumococcus Type I were found, and the blood culture was sterile. Serum taken immediately after giving the solution had power to protect a mouse against .0001 cc. of culture, the lethal dose for the controls being 0.0000001 cc. This protective power was maintained the following morning. Blood cultures were sterile.

Case 2. — Disappearance of Pneumococci from the Blood, Following an Injection.

H. D., male, aged 27, with pneumococcus Type I pneumonia, was admitted to the hospital on the 4th day of his disease. Blood was taken for culture and protective bodies, and then 10 cc. of Lot No. 8 were given intravenously. Four hours following the injection, blood was again taken for protective bodies. Before the administration, blood culture showed 10 colonies of pneumococcus Type I per cc., and no protective power; 4 hours after the injection, the blood protected against 0.001 cc. of pneumococcus Type I, 18-hour blood culture. No blood culture was taken; 20 hours later the blood culture was sterile and the protective power was maintained. Two doses consisting of 10 cc. and 5 cc. were given on the 5th day and on the 6th day the blood culture continued to be sterile and the protective power of the serum was maintained.

Case 3. — Persistence of Type II Pneumococcus in the Blood after an Injection of the Type I Refined Serum.

R. C., male, aged 28, pneumococcus Type II pneumonia, entered the hospital on the 5th day of his illness. On the following day, 2 doses of 10 cc. each were given. Before the 1st dose of serum, blood was taken for culture and protective bodies. This specimen was sterile and contained no protective bodies for pneumococcus Type I. The following day, 12 hours after the administration of the 2nd dose of 10 cc., blood culture showed 10 colonies of pneumococcus Type II per cc. At the same time, the serum showed protective bodies for pneumococcus Type I, to the extent of protecting a mouse against 0.0001 cc. of culture, the lethal dose being 0.00000001 cc. The patient became progressively worse, and died.

From these few experiments it seems clear that the Felton antibody solution administered intravenously in doses of 6 to 10 cc. gives protective character to the blood for pneumococcus Type I (of considerable concentration). The case of H. D. with the pneumococcus Type I bacteremia, which cleared up after the administration of 10 cc. of the blood, came about through the administration of F. R. P. S. The demonstration of protective bodies for pneumococcus Type I in the presence of bacteremia of pneumococcus Type I, shows the specificity of the immune serum for its own type, and the improbability that it has any measurable therapeutic effect on pneumococcus Type II pneumonia.

A COMPARISON BETWEEN THE HUNTOON ANTIBODY SOLUTION AND FELTON'S GLOBULIN SOLUTION

The fact that, after giving 6 to 10 cc. of F. R. P. S., it is possible to demonstrate it in the blood in the form of Type I protective bodies, offers a means of comparing its potency with that of antibody solution. In 5 pneumococcus Type IV pneumonias, doses of 50 cc. of the Huntoon antibody solution, given intravenously, failed to give any definite protective character to the blood for pneumococcus Type I, following administration. After the administration of 100 cc. of antibody solution to pneumococcus Type I pneumonia, definite protection for pneumococcus Type I has been demonstrated. Therefore, the ratio of concentrations of F. R. P. S. and antibody solution would seem to be approximately 6:100. This test, together with others indicated that the average F. R. P. S. is between 10 to 20 times as strong as the average Huntoon antibody solution, volume per volume.

REACTIONS FOLLOWING ADMINISTRATION

The following statement is quoted from Baldwin and Cecil, and is in accordance with my own less abundant experience:

> The reactions that accompany or follow the administration of Felton's solution when given intravenously, were studied along 3 lines. The first consisted of allergy and anaphylactic phenomena that occurred coincident with administration. The 2nd were the chills and consequent hyperpyrexia that occurred 30 minutes to 1 hour after administration. The 3rd consisted

in ascertaining the likelihood of serum-sickness developing following administration.

The presence of horse serum in the solution impelled us to do intradermal tests with horse serum before administration was begun, and to inquire whether the patient had recovered from doses of horse serum, in order that hypersensitivity might be determined. Patients were also asked whether they were subject to asthma or hay fever, to determine if possible a pre-disposition to allergy. Of the 29 patients treated, none gave positive intradermal reaction with horse serum, or, upon questioning, showed evidence of allergy. In this series 1 patient gave a severe allergic evidence response following the first dose, while another after an interval of 8 days between doses responded to the 1st dose after the interval with severe anaphylactic shock.

Detailed account of the two cases follows:

W. R., male, aged 50, entered the hospital on the 2nd day of his illness. Sputum showed pneumococcus Type I. The patient was a stout, well-nourished male, employed as a stationary-engine fireman. His face was cyanotic, and physical examination showed frank, though early, signs of consolidation in the right lower lobe. The conformation of his chest was that associated with emphysema. On the morning of the 3rd day of his illness, 5 cc. of Lot No. 5 was given intravenously and rather rapidly, the whole injection taking less than 1 minute to give At its conclusion the patient suddenly became deeply cyanosed, complained of splitting pain in the head, and had severe subnormal oppression, with inability to breathe. After 15 seconds these signs and symptoms disappeared. Adrenalin was not given. The patient returned to his previous condition, and seemed to feel no worse for the experience. No more F.R.P.S. was given.

J. J., male, a Porto Rican, aged 18, entered the hospital on the 2nd day of his illness, in good condition, appearing moderately ill. Sputum showed pneumococcus Type I. Signs of consolidation were found in the right upper and middle lobes. On the 3rd day of his illness, 2 doses of F.R.P.S., Lot No. 5, were given, consisting of 3 cc. and 4 cc. each. A temporary fall of temperature and clinical improvement caused treatment to be discontinued. Eight days following the first injection, the patient continued to have a fever, and signs of an active pneumonia persisted. Believing that the amount of horse serum in the solution was small, and that barely sufficient time had elapsed for hypersensitivity to develop, the patient was given very slowly a dose of Lot No. 8. Twenty seconds after the beginning of the injection and with less than 1 cc. given, the

patient suddenly became deeply cyanosed, uttered shrill cries, was unable to breathe and became incontinent of urine. A few medium sized rales were heard throughout the chest. This very grave condition of impending death continued for 30 to 45 seconds. Adrenalin was given subcutaneously and the acute condition abated, leaving the patient in a cold sweat and with a rapid pulse. Fortunately the patient had sufficient stamina to withstand the shock, and an uneventful recovery ensued.

THE INCIDENCE OF CHILLS

Following 53 injections of 5 cc. or less of Felton's solution given intravenously, there were 11 chill reactions. Among 28 instances in which more than 5 cc. was given (usually 10 cc.) 3 chill reactions occurred. Lots No. 5 and No. 8 were the least likely to be followed by chills and hyperpyrexia. There were only 8 chill reactions in a total of 47 injections of Lot No. 5, while in a total of 27 injections of Lot No. 8 there were only 2 chills. Only 3 injections of Lot No. 9 were given. One chill occurred. When Lot No. 3 was used, 3 injections of 5 cc. or less were followed each time by a severe chill. Preparations all seem to differ markedly in their tendency to produce chills. This same difference is noted with the antitoxic globulin preparations.

The character of the chills and hyperpyrexia when these reactions occurred, was very similar to that which usually followed the administration of Huntoon's antibody solution, but intravenously the reactions were less intense. About 30 to 40 minutes after injection the patient would go into a rigor which would last from 5 to 40 minutes. Following the chill the temperature would rise to 105 degrees or 106 degrees. Occasionally it reached 107 degrees. Then the patient's temperature would fall, a profuse sweat would occur, and subjectively there would be a feeling of well-being and repose. Usually the temperature would rise again, and, from observation of cases that had chills, it did not seem that the chill itself exerted any permanently beneficial therapeutic effect.

No cases of serum sickness resulted in the 30 patients treated with Felton's serum solution. Not even a single urticarial wheal has been observed among the treated cases.

METHOD OF ADMINISTRATION

The method of administering the solution consisted in giving 5 cc. to 10 cc. intravenously, using a luer needle and syringe. The solution was warmed to approximate body temperature. The first cc. was given very slowly, to prevent the danger of excessive allergic or anaphylactic shock. Usually about 60 seconds were spent in giving the first cc. Then, if the total dose was 5 cc., the remainder was given in the next 2 to 2½ minutes. If the total dose was 10 cc., 5 or 6 minutes were spent giving the injection. Adrenalin chloride 1/1000 solution was kept available for immediate use in case of shock. Five minims intravenously should be used.

THERAPEUTIC RESULTS

The therapeutic effect of administration of Felton's Type I concentrated serum has been observed in 35 cases of pneumonia. I quote from the notes of Cecil and Baldwin.

It is realized that the series is very small and that no controls were used. No attempt was made to treat only early cases. A few clearly moribund cases were excluded. After the first month of the experiment, when it was found that Type II and Types III and IV cases had shown no therapeutic response following administration, most of the cases treated were restricted to Type I pneumonias.

Of the pneumococcus Type I pneumonias receiving treatment, there were 19. Of these 1 died, a mortality rate of 5.6%. Clinical impression of the results obtained in treating the Type I pneumonias was distinctly favorable.

The following case reports, in brief, may be cited.

A. H., male, aged 15, pneumococcus Type I, entered the hospital on the morning of the 3rd day of his illness, with frank signs of consolidation on the right lower lobe. On the morning of the 3rd day, when his temperature was 103½, he received 5 cc. of F. R. P. S., Lot No. 5, intravenously, and in the afternoon a similar dose. The next morning the temperature was 102 degrees, and another dose of 5 cc. was given. In the evening of that day the temperature fell to 98 degrees. The following day the clinical condition was much improved and, while his temperature remained at 101 degrees throughout the day, it soon returned to normal.

No chills or hyperpyrexia followed any of the injections.

H. D., male, negro, aged 27, pneumococcus Type I, was admitted to the hospital on the 5th day of his disease, with frank signs of consolidation in the right lower lobe. This was reported among the cases used for identification of Type I protective bodies in the blood following administration. On the afternoon of the 5th day, blood cultures showed 10 colonies of pneumococcus Type I per cc. He was given 10 cc. of F. R. P. S., Lot No. 8. No chill occurred. The following morning the blood culture was sterile. The temperature remained elevated; 10 cc. of F. R. P. S., Lot No. 5, were given; 45 minutes later there occurred a severe chill which lasted 40 minutes, at the conclusion of which the temperature rose to 106.8 degrees and the patient became delirious. In the afternoon he was given 5 cc. of F.R.P.S., Lot No. 5, followed by a chill. The next day the temperature was still elevated, and restraints were required because of mild delirium; 8 cc. of F.R.P.S., Lot No. 9, were given in the morning. Following this injection a chill occurred which lasted 30 minutes, with a rise of temperature to 105 degrees as its conclusion; 3 cc. given in the afternoon produced no reaction. The following day the patient was clinically improved although his temperature still remained elevated; 6 cc. of Lot No. 8 were given, with no chill resulting. Signs of active pneumonic process began to subside, the condition no longer was critical and later on empyema was discovered.

J. S., male, aged 56, pneumococcus Type I, was admitted to the hospital on the 1st day of his illness. On the 4th day he was given 6 cc. of F.R.P.S., Lot No. 8. No marked change in the general picture of his disease occurred. The following day 4 cc. were given. No chills occurred after either dose. On the afternoon of this day the patient appeared better; the temperature fell, and on the morning of the 6th day of his illness there was no fever and the patient began to convalesce.

The one fatality among the Type I pneumonias was due to complications. The history of this case, and of a fatal case in which the serum was not given until after the recovery from the pneumonia, is as follows:

J. K., male, aged, 34, pneumococcus Type I, was admitted to the hospital on the 4th day of his illness, with frank signs

in the right lower lobe. On the 6th day, at noon, he was given 5 cc. of F.R.P.S., Lot No. 5. No chill followed. At 5 P.M. 7 cc. of Lot No. 5 were given, followed 1½ hours later by a chill, moderate in severity, lasting 10 minutes, and followed in turn by a rise in temperature to 105 degrees. At 11 A. M. 5 cc. of F.R.P.S., Lot No. 5, were given with no chill resulting. The following day, 2 doses of 5 cc. each of Lot No. 5 were given, neither of which was followed by chill. The last dose was administered on the 8th day, and consisted of 5 cc. of F.R.P.S., Lot No. 5. No chill occurred. The next day there was a break in the patient's temperature and considerable clinical improvement. The patient continued to run a low-grade fever, with questionable signs of fluid at the right base. On the 21st day of his illness, signs of pericarditis with effusion became evident. Operation was advised and performed. The patient rallied following the operation, but only temporarily, and four days later died.

CASE OF ARTHRITIS AND EMPYEMA FOLLOWING TYPE I PNEUMONIA WHICH SHOWED NO RESPONSE TO TYPE I FELTON'S REFINED SERUM

D. M., male, aged 53, pneumococcus Type I, was admitted to the hospital on the 7th day of his illness, with signs in the right upper and right lower lobes. His temperature, soon after admission, dropped to 101-100 degrees, and the pneumonic process had apparently subsided. At this time the left wrist became swollen and red; 3 days later the temperature had risen to 103 degrees and the patient was obviously more severely ill. Because of the possibility that a bacteremia might be present or develop, 3 doses of 8 cc. each of Lot No 8, were given during the next 24 hours. No chills occurred. The blood culture taken before these injections was sterile. Two days after the last dose of F.R.P.S., the temperature still remained up, although the Arthritis was subsiding. The patient was perspiring, the pulse was rapid and a moderate degree of cyanosis was present. Examination of the chest suggested fluid at the right base. Blood culture was taken on this day, and was positive for pneumococcus Type I. Two days later pus was aspirated from the right chest and operation was ad-

vised. This was refused by the patient. During the next 5 days, 5 doses of F.R.P.S. were given with little effect on the toxemia. Unfortunately no further blood cultures were taken. Finally, 8 days after his previous refusal to undergo an operation, consent was given and with the patient in semi-coma, intercostal drainage was performed. The patient died soon after the operation.

As a result of the treatment of pneumococcus-Type-I pneumonia, our impression is that when Felton's solution is given intravenously in doses of 5 to 10 cc. 1 or 2 times a day — preferably early in the course of the disease, and with caution as regards horse serum hypersensitivity — septicemia is prevented or overcome, the time of crisis or lysis is likely to be hastened and clinical improvement results. The only fatality among the 19 cases of Type I pneumonias treated was a case that was treated late in the course of the disease and died on the 25th day of complications.

No favorable influence from Type I, Felton's serum, was thought to be exerted upon pneumonococcus Types II, III, and IV pneumonias in the small number of cases treated. The results of numerous animal tests indicate that while there is slight cross-protection from specific highly potent serum, for one type from other types, it rarely amounts to more than 1% and is probably too slight to have any appreciable effect. It is necessary therefore to study in each country the dominant types of pneumococci and to prepare for each, if possible, a potent serum. These, after refining, can be combined to make a polyvalent preparation.

CONCLUSIONS

The pneumococci are divided into a number of types. Vaccination of an animal with any type causes its tissues to make a potent antibody for that type, but for no other. There is, it is true, slight cross-protection of a single type serum for other types, but this is insufficient for therapeutic effect. Intravenous injections of antibody, in a case of pneumonia, will prevent blood invasion of the type matched by this serum antibody and, with few exceptions, will sterilize the blood which has been invaded.

As cases of septicemia are the ones that usually do badly, this fact in itself strongly indicates that the antibody is of real value.

A large number of cases due to Type I infection have been treated with Type I serum. These show a considerably lower mortality than the average for untreated cases. The discovery of Felton eliminates from the serum most of the unprotective substance and so, in refining, removes the fear of serum sickness and, in concentrating, allows us to combine the antibodies of 3 or even 4 types into a potent polyvalent antibody solution. The antibody in the Felton refined serum is united to a globulin or is a globulin. The antibody solution should be given into the vein with the same care as the diphtheria globulin solution. With some preparations a moderate chill is frequent — with others infrequent.

Where it is possible to type the pneumococcus causing the pneumonia, this should be done. The first dose given would then be of the polyvalent antibody for Types I, II, III and any other dominant strain. The pneumococci causing pneumonia should be studied in each region so that there would be available the type antibodies needed for the cases.

It is perfectly possible that places other than in South Africa have a considerable percentage of pneumonia due to a type which is not I, II or III. While it is true that up to the present time Type I cases have seemed to respond to Type I serum, better than Type II cases to Type II serum and Type III cases to Type III serum, still it seems to me to be probable that this may be due partly or largely to lesser potency of the Type II and Type III serums. Felton's discovery makes practicable to have a highly potent antibody solution for any type of pneumococcus. The potency of every preparation for the types it is intended for, should be indicated on each vial. To make this practicable, a standard unit should be adopted, which if possible should be a world unit and not a sectional one.

DISCUSSION

Dr. Milton J. Rosenau (Opening the Discussion). — I am very sorry that Dr. Felton is not here personally to respond to the request to discuss the production and constitution of his anti-pneumococcus solution.

Dr. Felton approached the problem from the standpoint of virulence. He had been working on the subject of virulence, especially the factors that influence the virulence of pneumococci, for a number of years. He discovered that pneumococci grown in normal horse serum maintain their virulence very well, but when grown in anti-pneumococcus horse serum they lose their virulence quickly. Conceiving that there must be some substance in the anti-pneumococcus serum which gives this decline, he set about looking for that substance, seeking it among the globulins, and after trying all the known methods, he finally hit upon the method of dilution. When anti-pneumococcus serum is diluted with water, a heavy precipitate comes out which may be collected, washed and dissolved. The process may be repeated a number of times until the precipitate is obtained in a high degree of purity. This substance carries with it all the protective properties contained in the original solution. It is a euglobulin and therefore at once distinguishable from diphtheria anti-toxin, which is in the pseudo-globulin fraction. It is not as yet clear whether the antibodies are euglobulins or attached to the euglobulins, but whichever it is the solution is obtained in a high degree of purity and concentration. We therefore have a solution carrying all the properties of an anti-pneumococcus serum without the foreign proteins and other undesirable substances in horse serum.

Experimentally in animals, Felton's antibody solution has both protective and curative virtues in comparatively small amounts. Clinically in human cases, it has given encouraging results, as Dr. Park has intimated, but it will have to be tried over a long period of time on many cases of pneumonia before its limitations and effectiveness can be determined. The antibody solution is specific, but a specific solution is readily obtained for each one of the fixed types. There is therefore good reason to hope that at last we have something that will be essentially beneficial in pneumonia.

Dr. H. J. Nichols. — I want to say that I think we are all indebted to Dr. Park for his work in vaccination, even if his results are negative. We have had the same experience in the Army, so that we feel some sympathy. In regard to the serum, we had one epidemic of Type I pneumonia among the troops on the Mexican border in 1916. We used this serum, and I ventured at that time to state that any one who died of Type I pneumonia without Type I serum had not received all the attention that scientific medicine had to offer. The mortality was reduced from 30% to 7% by use of the serum. We couldn't always get it, as it came from New York, and whenever the supply ran out, the funerals increased and

all was gloom around the place. When the new supply arrived, the clinicians cheered up immediately and everything was encouraging.

It is sufficient to say, about vaccination in the Army, that we tried the ordinary organisms and when it was announced from the Rockefeller Institute that *B. pneumosintes* was possibly the cause of influenza, we tried this. An influenza epidemic came along and it picked out the vaccinated individuals immediately. The officers who gave us best support were the first to come down and with the most serious cases. While the experience does not prove that this organism is not the cause of influenza, it gives no support to the claim that it *is* the cause.

I should also like to mention vaccination by mouth. This hasn't been emphasized in connection with influenza but it has in connection with typhoid. We have done some work on the subject in the Army Medical School, on some of the natural diseases of guinea pigs, using paratyphoid B. We took 6 guinea pigs and vaccinated them in the ordinary way subcutaneously, and after a period of 2 or 3 weeks gave them a dose of this organism by mouth. We used a ureteral catheter passed into the stomach. One of these pigs became infected and died of the organism. The other 5 were not affected. We also had 6 pigs vaccinated by mouth. We gave bile and then gave vaccine about 3 hours later. The process was repeated in 3 days, according to instructions. The pigs were later infected by mouth, and all took sick and died of the disease.

This is just a little laboratory experiment on this problem, but it is suggestive, and if any one should ask me at present about mouth vaccination for typhoid, I should say that if he cares to substitute an uncertainty for a certainty he might try it. Subcutaneous vaccination is more or less of a certainty — the oral method is not yet proved. Patients may like the oral method but it is an uncertainty.

If we had a considerable influenza epidemic today I think the only advances we should be able to put into effect as compared with methods during the last epidemic, are, first, that the patient would be kept in bed instead of being allowed to get up after a few days; and secondly, we might use the convalescent influenza serum in combating infection. Otherwise we should be helpless.

Major George C. Dunham. — In the fall of 1921, we attempted to make a study of the mixed pneumococcus vaccine, to determine whether it was of value in the prevention of common respiratory disease. The vaccine used consisted of Type I, Type II and Type III pneumococcus, the influenza bacillus, and the streptococcus bacteria. A number of stations were selected, about 20,000 per-

sons being involved in this study; 6,000 were given the vaccine and the others were used as controls. The results were negative, except possibly in a group of soldiers who had been in the service only a short time, less than a year. The vaccine apparently conferred some little resistance to respiratory diseases among the members of this group. On the whole, the results were insignificant; they did not indicate that vaccine had produced any real protection against respiratory infection.

Dr. William Halleck Park (*Closing the Discussion of His Own Paper*). — Our experimental work on animals — as regards the results of mouth-feeding of vaccine — corresponds to that described by Major Nichols. I suggest that all who use anti-pneumococcus serums try to induce the manufacturers to indicate the units of antibody strength. With the old serum the doses were so large, and there was so much doubt about the value of the serum, that the manufacturers were permitted to label the serum as up to standard potency. Having a refined serum, which I am sure we can advocate for Type I and I hope we can advocate for Types II and III, I think we should have an international unit of strength in order that we may all have the same measure, and so be able to compare our results. There are 2 ways in which we now measure potency — namely, (1) the number of fatal doses of very virulent pneumococci that .2 cc. of serum will protect, or (2) the amount of serum that will protect a white mouse against 1,000,000 fatal doses. Both methods have advantages and drawbacks.

TELA RAILROAD HOSPITAL AT TELA, HONDURAS

REAR VIEW—FOLIAGE PREVENTS OBTAINING SATISFACTORY FRONT VIEW

PROPHYLACTIC VACCINATION AGAINST LOBAR PNEUMONIA

WILLIAM H. PARK, M.D.

The results following vaccination of small animals clearly establish the fact that antibodies are produced by vaccination. These protect them from infection with the same type of pneumococci they received in the vaccine. This immunity is at its highest point some 7 to 10 days after the injection, and then slowly diminishes. In many tests we have found that although there is slight cross-protection in a highly immunized animal for other types than those used in the injection, this is never enough to be of practical importance. We have made interesting tests of the comparative value of freshly prepared and long-stored vaccines, and of vaccine made from freshly isolated and long-cultivated strains, and found them all effective to stimulate the abundant production of antibodies in animals.

When we come to test the practical value of pneumococcus vaccine in man, we meet greater difficulties. According to the locality, only about 50 to 80 per cent of cases of lobar pneumonia are due to the 3 most dominant types. The remaining 20 to 50 per cent of the cases are therefore without the scope of the vaccine, for it is impracticable to use more than 3 types in a vaccine. Even for the standard types it is not practical to give more than 3 injections of moderate size. This is because of both the expense and the objections to the reactions from those we would protect. It is not yet certain whether the antibodies which will develop after 3 injections are sufficient in amount to give in the great majority a temporary protection against the types utilized. In many parts of the world during the past 15 years vaccination has been carried out, and the reports are almost universally favorable.

The most extensive test known to me was the one begun by Wright, in South Africa, and finished by Lister. The latter typed the strains of pneumococci and made a vaccine of the dominant strains. The work lasted from 1912 to

1915 and, according to the reports, pneumonia lessened immediately after the beginning of the vaccination. He gave large doses, using 6,000,000,000 of each of the 3 varieties in each injection. In spite of the use of pneumococcus vaccine on a large scale in the World War, and the advertisement of its value by producers of biological products the use of the vaccine has never been generally accepted and put into general practice. My own investigations on this subject were begun because the members of the Influenza Commission of the Metropolitan Life Insurance Company thought some carefully controlled tests should be made.

The actual carrying out of the tests was done by Doctor Anna Von Sholly.

The first test was the vaccination of 1,536 employees of the Metropolitan Life Insurance Society. In October, each of these workers received 3 injections. Each dose contained 6,000,000,000 pneumococci, divided equally between the 3 types, and to them were added 2,000,000,000 of streptococci and 1,000,000,000 of influenza bacilli. The latter two were given in a futile attempt at immunizing against common colds. Daily reports were made as to the health of these and the 3,025 people who volunteered as controls. During the 5 months following the injections, 11 lobar pneumonias developed among the unvaccinated, or 0.36 per cent and only 1, or 0.06 per cent in the vaccinated. As the group of the unvaccinated was more than twice as large as the vaccinated, this was a proportion of 6 to 1. During the next 3 months there were no pneumonias among the unvaccinated, while 2 occurred among the vaccinated. This made the cases a proportion of 2 to 1. Leaving out of consideration the comparatively small numbers, the results of this experiment suggested that the vaccine had caused in many immunization against pneumococcus infections, and that this had at least partially disappeared at the end of 5 months.

We were encouraged to continue the investigation. As the Metropolitan Life employees objected to a repetition of the injections, we arranged to continue the tests on the inmates of the Asylum for the Insane at Wards' Island. In order that there might be no differences between the treated and the untreated cases, all the inmates were carefully ex-

amined, and 3,500 were found to be comparatively fit, and about 1,500 were found to be too ill to be suitable for the test. These latter were excluded. The others were divided into equal groups. Those who comprised one half received 3 injections each containing 9,000,000,000 pneumococci; the types I, II and III were equally represented. The other half of the employees were kept as a control. As new admissions were received, they were carefully examined and divided among the 3 groups. These injections were repeated in the great majority of the treated patients every 6 months during the past 3 years. The injected, the controls, and those excluded because of poor health were all kept under observation.

Lobar pneumonia cases in the vaccinated the first year were 3, in the unvaccinated 6.

The next year there were 2 cases in each half, and in the third year there were 7 in the vaccinated and only 4 in the unvaccinated. In each half in the treated and the control portions there were therefore exactly the same number of cases; 9 of the 12 who developed lobar pneumonia after vaccination had received their vaccine within 5 months of the attack.

The acute Broncho-pneumonias were 14 among the vaccinated, and 16 among the unvaccinated. The terminal pneumonias were 28 among the inoculated, and 24 among the uninoculated. Only about one-third of the cases of Lobar pneumonia could be typed. Type III pneumococci and those of the Type IV group were each found to the extent of about 40 per cent, the Type I and Type II cases making only 20 per cent. The results from the 3 years' test were disappointing, in that they showed no appreciable effect of the vaccine.

The peculiar type of the population of the Institution and the predominance of pneumonias due to Types III and IV pneumococci may have had much to do with the lack of result. An interesting fact developed, that while among the average number of about 3,600 inmates selected because of their being in fair health, only 101 developed pneumonia (0.028 per cent) yet there were 89 (0.055 per cent) among the 1,600 put aside as unfit for the test because of chronic ill health or senility. These latter developed an excessive

number of cases of terminal pneumonia. About one-half of all the cases were terminal infections and much more than one-half of the deaths due to pneumonia were in this group.

The fact that the result was so favorable for the first 5 months after vaccination among the employees of the Metropolitan Life Insurance Company,— when considered in connection with other favorable reports — suggests that vaccination of healthy young adults gives protection for a short time against lobar pneumonia due to the fixed types. The terminal and Broncho-pneumonias on the other hand, especially when they occur as complications of other diseases, are probably prevented but little, if at all, by vaccination.

HAEMORRHAGIC BRONCHITES OF NON-TUBERCULAR ORIGIN

ALDO CASTELLANI, M.D.

Since 1903, both in the Tropics and in the temperate zone, I have endeavored to call attention to a group of parasitic bronchial and broncho-alveolar conditions, which clinically in many cases closely simulate pulmonary tuberculosis, though not of tubercular origin. Some of these affections are limited to the Tropics, but others are found also in temperate zones, and during the last 7 years I have observed several cases in various parts of the Continent and in England. The aetiology of these affections is varied, the causative agents being as far different as protozoa, worms and fungi; they may be separated into 2 groups: those of animal origin, or *broncho-zoiases*, and those of vegetal origin, or *broncho-mycoses*. The classification I have suggested is the following:

- A. Due to animal parasites (*Broncho-zoiases*)
  - (1) Protozoa
    1. *Broncho-spirochaetosis*
    2. *Broncho-amoebiasis*
  - (2) Metazoa
    Broncho-Paragonomiasis
- B. Due to vegetal parasites (*Broncho-mycosis*)
  - (1) Fungi imperfecti
    1. *Broncho-nocardiasis*
       Synonyms
       - *Broncho-streptothricosis*
       - *Broncho-cohnisstreptothricosis*
       - *Broncho-actinomycosis*
       - *Broncho-discomycetosis*
    2. *Broncho-anaeromycosis*
    3. *Broncho-moniliasis*
    4. *Broncho-cryptococcosis*
    5. *Broncho-hemisporosis*
    6. *Broncho-sporotrichosis*
  - (2) Ascomycetes
    1. *Broncho-saccheromycosis*
    2. *Broncho-endomycosis*
    3. *Broncho-oidiosis*
    4. *Broncho-aspergillosis*
    5. *Broncho-penicilliosis*
    6. *Broncho-acremoniellasis*
    7. *Broncho-cladosporiosis*
    8. *Broncho-accladiosis*
    9. *Broncho-sporotrichosis*
  - (3) Phycomycetes
    Broncho-mucocormycosis

BRONCHO-SPIROCHAETOSIS

The history of *Broncho-spirochaetosis* is, briefly, the following: — In 1905, in Ceylon, two natives came to consult me for recurrent *haemotysis*. I kept them under observation for many months, but never succeeded in finding the tuberculosis bacillus. The sputum, instead of the bacillus of tuberculosis, contained an enormous number of spirochaetes; in fact, in the bloody portions of the expectoration these parasites were practically the only organisms present. The spirochaetes almost completely disappeared during periods of quiescence, to reappear again in huge numbers every time the symptoms became acute. I came, therefore, to the conclusion that there was probably a form of hemorrhagic bronchitis of spirochaetic origin. Later, I came across many other cases, and my work was confirmed by Branch in 1907 in the West Indies, and by Jackson in 1902, and in the Philippine Islands. In 1909 Waters described numerous cases of the disease occurring in India, and Phalen and Kilbourne a case in the Philippine Islands where, in 1911, Chamberlain recorded 2 more cases.

In 1913 Chalmers and O'Farrell carried out an investigation on the malady in the Sudan, and succeeded in reproducing it in a monkey. In 1914 Taylor investigated the condition in Uganda. In 1915 Fantham published a classical paper on *Spirochaeta bronchialis*, studying it completely from a morphological point of view, and described its granular stage and the intracellular forms of the parasite.

In the same year Macfie reported cases from West Africa, and Galli-Valerio recorded several interesting cases of the malady in Switzerland, and Lurie and myself one in Serbia. In 1917 Galli-Valerio recorded other cases in Switzerland. In 1917, Violle first noted the affection in France, and published numerous papers on it. Violle's observation stimulated further research in France, and a number of cases were reported by Bine, Dide, and Ribereau, by Netter, Dalimier, Barbary, and others. In 1919 Farah described several cases in Egypt, and Alcock a case occurring in a British soldier, in Northern Italy. Villa, and Corvetto and, more recently, many other observers have recorded cases in South America; Clark and Facio in Central America;

Mendelson in Siam; Levy, Bloedorn, and Houghton in North America; Broughton, Alcock, and Browne in England; and Iacono, Trocello, and others in Italy. Recently an interesting communication on *Broncho-spirochaetosis* in China has been published by Faust; Mouchet and Van Nitsen have found the disease in Katanga, and De Mello and De Andreds have reported cases from Portugal. Special mention must also be made of the important, very complete, paper by Farah in the "Journal of Tropical Medicine," April 2, 1923.

Geographical distribution. — The disease has probably a cosmopolitan distribution. It has been found in Ceylon, India, Philippine Islands, China, and Indo-China, North and Equatorial Africa (North and South), and Central America, and recently in practically every European country, including Great Britain.

Spirochaeta bronchialis Castellani, 1907. — The spirochaete which I found in 1905, and which I named *Spirochaeta bronchialis*, has been investigated by numerous observers and principally by the well-known protozoölogist, Professor Fantham, who described the coccoid and the intracellular shape of the organism.

The spirochaete is extremely polymorphic; its length varies between 3 and 30 microns, its breadth between 0.2 and 0.6 microns. Fantham states that of 2 principal types found: those 7 to 10 microns, and those between 14 and 16 microns, he believes that the former originate by a transverse division from the latter.

Spirochaeta bronchialis, according to Fantham, Chalmers, and O'Farrell and Taylor, differs from the common mouth spirochaete in the following points:

1. It is more actively motile.
2. It dies very quickly in fresh preparations of sputum, while the oral spirochaetes may live for hours outside the human mouth.
3. It is stained with more difficulty.
4. According to Fantham there is an intracellular stage, which is absent in the oral parasites.

Predisposing causes. — A chill often acts as an important predisposing cause.

Experimental reproduction. — Chalmers and O'Farrell re-

produced the disease in monkeys; attempts to infect guinea pigs and rabbits failed.

Method of Infection.—Probably infection takes place from infected to healthy persons, the spray exhaled in coughing being contaminated with the spirochaetes, or, as Fantham believes, with the resistant coccoid bodies. It is also possible that a certain number of persons may harbour *Spirochaeta bronchialis* in small numbers, and that a chill may decrease the organic resistance of the carrier and increase the virulence of the organisms in a way somewhat similar to what is the case with the pneumococcus and other microörganisms.

Symptomatology. — According to my observations, 3 principal types of the disease may be distinguished:

The acute type
The sub-acute type
The chronic type

Acute Broncho-spirochaetosis. — This type at times resembles influenza; the *onset* is often abrupt, the patient feeling chilly and complaining of rheumatoid pains all over the body, and developing fever which generally is not very high, rarely exceeding 103 F. The fever may last between 2 and 12 days. The patient coughs a great deal and the expectoration is scanty, muco-purulent, and very occasionally containing traces of blood. In most cases the general condition of the patient is not affected; in others, there is great prostration.

Sub-acute Broncho-spirochaetosis. — The attack begins either suddenly or gradually and lasts between 2 and 12 weeks. In some cases there is fairly high fever, in others the temperature is practically normal and the general condition of the patient may remain satisfactory. The cough is frequent and there may be expectoration of pink jelly-like mucus, and true *haemoptysis* may take place. The physical examination of the chest may reveal nothing at all, or only signs of simple bronchitis; but at times patches of slight dullness with crepitations may be observed. The blood may show a slight degree of anaemia; as a rule, the number of leucocytes is normal, and so is the differential leucocyte count.

Chronic Broncho-spirochaetosis.— Chronic bronchial *spirochaetosis* may follow on an acute or sub-acute attack or several

such attacks, but frequently the *onset* is quite insidious and slow. The patient has a chronic cough, which is at times more severe in the morning. Sometimes genuine attacks of *haemoptysis* occur, one or two teaspoonfuls or more of blood being brought up. In some cases there is no fever, in others a serotine, true-hectic-like fever may be present. Occasionally the rise in temperature takes place in the morning, and not in the afternoon; in other cases the temperature chart is most irregular. The physical examination of the chest reveals very little except a few coarse râles. In some cases there are clear signs of a patchy consolidation. The general condition of the patient may remain fairly good for a long time, though a certain degree of anaemia is often present. A few cases waste rapidly.

The course of the disease may be prolonged, with periods of great improvement and even apparent cure. The 2 original cases I saw in Ceylon in 1905 were still alive when I left the island in 1915.

Two varieties of the chronic type may be mentioned: the *purulent* type and the *asthmatic* type. In the purulent type the patient has at times high intermittent fever, and coughs up a very large amount of purulent expectoration occasionally mixed with blood.

In the *asthmatic variety*, to which special attention has been paid by Farah, the patient shows signs of chronic bronchitis and now and then has an attack of typical asthma.

ILLUSTRATIVE CASES

To avoid the personal equation, I will quote a case thoroughly investigated by Bloedorn and Houghton, and published in the "Journal of the American Medical Association," Vol. 76, No. 23; also a case described by Iacono in the "Journal of Tropical Medicine," March 15, 1920.

CASE 1 (*Bloedorn and Houghton*). — A white man, aged 18, unmarried, was admitted to the hospital complaining of headache, pains in the back and shoulders, weakness, cough, and expectoration of blood-streaked mucus. Temperature 103, pulse 96, respiration 20. Teeth in good condition, no exudate on tonsils. Heart negative. Examination of the lungs disclosed only a few scattered rales at both bases, no impairment of resonance.

Clinical course. — The patient continued to have fever with temperature varying from 100 to 102 in the morning, and 103 to 104.3 in the evening. Profuse night-sweats occurred with great regularity, and the patient during the first 3 weeks of his illness lost 20 pounds.

There was a slight cough and rather free expectoration of a thin, muco-purulent, blood-streaked sputum. The prostration during the course of the disease was not marked, and the patient stated that he felt fairly well, but weak. The case resembled so strongly, in its clinical course, a pulmonary tuberculosis, that every effort was made to confirm such a diagnosis. The laboratory findings, Roentgen-Ray findings, and physical examination, however, failed to demonstrate the existence of such an infection. Wassermann and Noguchi negative. During the course of the repeated sputum-examinations it was noticed that, while the sputum was negative for tubercle bacilli, there were constantly present a large number of spirochaetes.

The presence of these organisms was at first not regarded as significant, and it was only after repeated attempts to establish a definite diagnosis in this case that their presence was regarded seriously. Their constant presence in the sputum after the teeth had been cleaned and the throat cleared with a mild antiseptic gargle, together with the absence of a lesion of the tonsils or pharnyx which might account for their presence, appeared significant and strongly suggested the diagnosis of "bronchial *spirochaetosis*."

It was decided to try the effect of an arsenical spirochaeticide, and on the 20th day 0.6 gm. of neo-arsphenamin was given intravenously, and on the 21st and 22nd days the temperature again rose to 101 in the evening. On the 24th day 0.5 gm. of neo-arsphenamin was given intravenously, following which injections of 0.9 gm. of neo-arsphenamin were given at intervals of 1 week, although the patient had shown no rise of temperature in the meantime, and was steadily improving. Following the injections of neo-arsphenamin the improvement in the patient was striking. The prompt termination of the fever, the rapid decrease in the number of spirochaetes and their ultimate complete disappearance from the sputum, the prompt cessation of the cough, and the disappearance of the blood from the

expectoration, which itself became almost negligible in quantity, leave little room for doubt regarding the efficacy of these injections.

Two months following the onset of the disease, the patient had regained his loss of 20 pounds, had been up and about for several weeks, and was able to resume his original duties. Before discharge from the hospital he was given an injection of 10 mg. of tuberculin, following which he showed no reaction.

CASE 2 (*Iacono*). — Miss E. B. No previous disease of importance. Present illness began 11 days before I saw her, with general malaise, rheumatoid pains all over the body, and dry cough. The fever remained high and continued for several days, then it dropped in the morning and assumed a serotine type. Rather suspicious subcrepitant rales were found, upon physical examination of the chest, in the left apex, and this fact, together with the serotine fever and sputum tinged with blood, led the family doctor to suspect tuberculosis of the lungs. When I was called in, the patient was very pale and feeling very weak; upon examination of the chest, no zones of dullness were found. Moist and dry rales were present all over, but no crepitant ones. Pulse 90, pressure rather high. Heart normal. As regards the abdominal organs, the spleen was not enlarged, liver just palpable. Urine contained a trace of albumin, and there was a slight increase in the phosphates, and indican. Blood: red-blood corpuscles, 4,000,000 per cm.; leucocytes, 9,000; haemoglobin, 70 (Fleischl). As to the leucocytic formula, there was an increase in the eosinophiles and lymphocytes. No malaria parasites and no spirochaetes were found. Examination of the sputum for tubercle bacilli, negative. Several glucose-agar tubes were inoculated, but no fungus was grown. The microscopical examination of films from the sputum stained with Giemsa, revealed presence of a large number of spirochaetes of variable length, 5 to 20 microns, and with 3 to 6 undulations. In fresh preparations examined with the ultra-microscope, numerous very motile spirochaetes were seen. I made a diagnosis of *broncho-spirochaetosis* and prescribed the mixture recommended by Castellani, the formula of which is: —

Tartar emetic	gr iii
Syr. tolu	ʒi
Aq. chlorof	ad ʒiii

1 teaspoonful in water every 2 hours.

This treatment had a very satisfactory effect, as within 3 days the serotine fever stopped, and after less than 3 weeks all the bronchial symptoms disappeared, and the patient's general condition of health became quite good.

Complications. — The disease may be complicated with tuberculosis, *broncho-mycosis*, and *rhinitis;* pneumonia and broncho-pneumonia have also been observed.

Diagnosis. — The diagnosis of *broncho-spirochaetosis* is based on the microscopic examination of the expectoration, collected after the rinsing of the mouth and gargling with sterile water. The sputum should be examined fresh, using the dark-ground illumination; or may be stained, using one of the modifications of the Romanowsky; or nitrate of silver staining methods, such as the Fontana-Tribondeau, may be employed. The sputum is teeming with spirochaetes, while bacteria are few or absent. The spirochaetes greatly decrease in numbers, or completely disappear, when the bronchial condition inproves.

Differential diagnosis. — The acute type is often mistaken for influenza or malaria. The examination of the sputum in which no Pfeiffer bacilli are found will distinguish the affection from influenza, and the examination of the blood will exclude malaria.

Cases of the *sub-acute* and *chronic* types presenting blood in the expectoration are generally diagnosed as *phthisis.* The examination of the sputum for tuberculosis bacilli will be negative, and the animal inoculations will remain without effect. The ophthalmo and cuti-reactions are negative in the great majority of cases. Occasionally, however, cases of mixed infection of tuberculosis and *spirochaetosis* occur. From *broncho-mycoses* the affection is distinguished by the absence of fungi; cases of double infection, however, *broncho-spirochaetosis* and *broncho-mycosis* may at times be observed, though rarely.

Spirochaetosis is easily distinguished from endemic *haemoptysis* by the examination of the sputum, which will show absence of the ova of *Paragonimus ringeri Cobbold.*

Prognosis. — The prognosis is favorable *quoad vitam*, but the disease may take a chronic course with occasionally severe anaemia and wasting.

Treatment. — In *acute* cases complete rest in bed with the administration of small doses of aspirin and a codein-tartar emetic mixture, is generally sufficient to bring about a cure.

In *sub-acute* and *chronic cases* tartar emetic and arsenical preparations, and occasionally potassium iodide, give good results. When the expectoration is profuse, glycerophosphates and balsamics (creosote) are useful. In severe cases, especially when the fever is high, salvarsan and neo-salvarsan given intravenously are often efficacious, as demonstrated by Galli-Valerio, Blordorm and Houghton, and others. Dalimier recommends intramuscular injections of camphorated oil with gomenol in acute cases, and Liquor Fowleri in cinchona wine in chronic cases. A change of climate is of advantage.

Formulae. — The following formulae will be found useful:

1. Tartar emetic ..... gr. ¼ to ½
   Sodii bi-carbonate ..... gr. x
   Glycerine ..... ℥i
   Aq. ad. 1 ounce ..... ℥i
   Sig. ℥i t. d.

2. Tartar emetic ..... gr. v.
   Sodii bi-carbonate ..... gr. xxx
   Glycerine ..... ℥i
   Aq. chlorof. ..... ℥i
   Aq. ad. ..... ℥iii
   Sig. 1 teaspoonful t. d. well-diluted in water.

3. Tartar emetic ..... gr. 1/6 to ¼
   Codein ..... gr. 1/6 to ¼
   Syr. tolu ..... ℥i
   Aq. chlorof. ad. ..... ounce 1
   Sig. ℥i t. d. well-diluted in water.

4. Tartar emetic ..... gr. 1/6 to ¼
   Potass. iodide ..... gr. v.
   Sodii bi-carbonate ..... gr. x.
   Glycerine ..... ℥i
   Syr. tolu ..... ℥i
   Aq. chlorof. ad. ..... ounce 1
   1 ounce t. d. well-diluted in water.

5. Liq. *arsenicalis* ..... mii-miii
Tartar emetic ..... gr. ⅙ to ¼
Codein ..... gr. ⅙
Glycerine ..... ʒi
Syr. tolu ..... ʒi
Aq. chlorof. ad ..... ounce 1
1 ounce t. d. well-diluted in water.

6. Sulphur ..... gr. iii
Pul Ipecaquace Co. ..... gr. ½
Duotal ..... gr. x.
Sodii benzoate ..... gr. x.
Fiat pulv. .....
1 powder t. d. .....

7. Tartar emetic ..... gr. iii
Syr. tolu ..... ʒi
Aq. chlorof. ad ..... ʒiii
1 teaspoonful in water every 2 hours.

BRONCHO-AMOEBIASIS

Chalmers and I some years ago called attention, in Ceylon, to a form of bronchitis, occasionally haemorrhagic, met with not very rarely in patients who were or had been suffering from amoebic *hepatitis*; and we noticed that ipecachuana in large doses caused a disappearance of both the bronchial and the hepatic symptoms. Other observers came across similar cases. In 1923 Petzetakis described, in Egypt, cases of primary amoebic bronchitis in which there was no history of dysentery and no history of *hepatitis*. His work was confirmed and enlarged by Ramond, Denoyells, Lautman, Panayotatou, and others. These cases show the symptoms of a rather severe bronchitis, the expectoration is mucopurulent, at times tinged with blood, occasionally some *haemoptysis* occurs. The diagnosis is based on the microscopical examination of the sputum, which will show presence of amoebae of the *histolytica type*. The beginner should be careful not to mistake for amoebae some macrophage leucocytes. *The prognosis*, provided the correct diagnosis is made in time, is good, emetine being a specific.

BRONCHO-DISTOMIASIS

(*Endemic Haemoptysis.*)

In 1880 Baelz, in Japan, noticed peculiar oval bodies in

certain cases of *haemoptysis*. He believed they were *psorosperms*, and called the condition *Gregarinosis pulmonum*. In the same year Manson found the same structures in a case of *haemoptysis* in a Chinaman from Northern Formosa, and a little later in a Portuguese also in Northern Formosa; and Ringer, who made the post-mortem, found in the lungs a minute, fleshy, oval body, grey in color. He forwarded it to Manson, the latter sent it to Cobbold, and he named it *Distomum ringeri* Cobbold.

In 1914, Nakagawa found that the parasites developed in the mollusc *Melania libertina* (Gould) and other species of the genus *Melania*, and that they encysted on the gills of certain crabs, *Potamon obtuspies*, *P. dehadni*, etc. Dogs fed upon these crabs showed eggs within 90 days after infection. Iturbe found that the *Distoma ringeri* found in South America develops in a snail *Ampullaria luitostoma* and some land crabs.

Geographic distribution. — The disease is found in Formosa, Japan, Corea, China, Sumatra, and recently it has been found also in South America, in Peru and Ecuador.

Symptomatology. — The patient complains of pain in the chest and a troublesome cough. The expectoration is mucopurulent, generally blood-stained. The physical examination of the chest reveals in most cases very little, — a few coarse rales. In other cases there may be signs of bronchopneumonia.

Diagnosis. — This is based on the microscopical examination of the sputum, which will show presence of the eggs; these are oval in shape, with a length of 0.08 to 1 millimeter.

Treatment is unsatisfactory. Tartar emetic has been tried without any satisfactory results.

BRONCHO-MYCOSES

Affections of the bronchi and lungs, associated with the presence of fungi in the sputum, are not at all rare, though comparatively little attention has been paid to them till recently. These conditions may be due to a variety of fungi, belonging to different species, genera, families, and orders, but from a practical point of view may be classified as follows:

1. Due to fungi of the genus *Nocardia* Toni and Trevisan, 1899, *Cohnistreptothrix* Pinoy, 1911, and *Anaeromyces* Castellani, Douglas and Thompson, 1921.

2. Due to fungi of the genus *Monilia* Persoon, 1797; *Oidium* Link, 1809; *Saccharomyces* Meyen, 1833; *Willia* Hansen, 1904; *Cryptococcus* Gilchrist and Stoker, 1896; *Coccidioides* Rixford and Gilchrist, 1898.

3. Due to fungi of the genus *Hemispora* Vuillemin, 1906.

4. Due to fungi of the genus *Aspergillus*, 1729; *Sterigmatocystis* Cramer, 1869; *Penicillium* Link, 1908; *Mucor* Micheli, 1729; *Rhizomucor* Lucet et Constantin, 1900; *Lichtheimia* Vuillemin, 1904.

5. Due to fungi of the genus *Sporotrichum* Link, 1809.

6. Due to fungi of the genus *Acladium* Link.

7. Due to fungi which have not yet been classified.

The symptoms are somewhat similar, whichever fungus is the aetiological factor. In mild cases there are signs of slight bronchitis with muco-purulent expectoration, in which the fungi are found. In severe cases the patient presents all the symptoms of *phthisis*, with hectic fever and haemorrhagic expectoration. Mild cases may get cured spontaneously; but they are often benefited by potassium iodide.

The prognosis varies a great deal, according to the causative fungus; the cases due to *nocardia* have the worst prognosis.

I will briefly describe a few of the *broncho-mycoses* I have mentioned, viz.; *broncho-nocardiasis*, *broncho-moniliasis*, *broncho-haemisporosis*, and *broncho-anaeromycosis*.

BRONCHO-NOCARDIASIS

Broncho-nocardiasis is the modern term used to denote all bronchial and broncho-pulmonary affections due to fungi of the genus *Nocardia*, Toni and Trevisan, and the genus *Chonistreptotrix* Pinoy which were previously more commonly known as *Streptothrix*, *Actinomyces*, *Discomyces*, *Oöspora*.

Two types of *broncho-nocardiasis* may be separated. One is characterized by the presence of fungal granules (*sclerotia*) in the sputum — *granular broncho-nocardiasis*.

In the other type no such granules are present — *Agranular broncho-nocardiasis*. The first type is still often referred to as *Actinomycosis bronchialis*, or *pulmonalis* and the second type as *Pseudo-actinomycosis bronchialis* or *pseudo-actinomycosis pulmonalis*. Before proceeding with the subject, it may be of advantage to give a few botanical data on

the nocardial fungi. These fungi belong to the order *Microsiphonales*. This order is characterized by the mycelium being composed of fine bacilliform hyphae, usually 1 micron or less in diameter. They are, as a rule, gram-positive when young, and without distinct nuclei; they are parasitic or saprophytic.

The order *Microsiphonales* has the following families:

A. *Nocardiaceae* Castellani and Chalmers, 1918 (Synonyms, *Actinomycetes* Lachner-Sandoval, 1898; *Trichomycetes* Petrusky, 1903).
Definition. *Microsiphonales* with a mycelium.
Type Genus. *Nocardia* Toni and Trevisan, 1889.

B. *Mycobacteriaceae* Miehe, 1909.
Definition. *Microsiphonales* without a mycelium.
Genus 1. *Mycobacterium* Lehmann and Neumann, with the diphtheria bacillus as a type.
Genus 2. *Corynebacterium* Lehmann and Neumann with the tubercle bacillus as a type.

FAMILY NOCARDIACEAE

Synonyms. *Actinomycetes* Lachner-Sandoval, 1898; *Trichomycetes* Petrusky, 1903.
Definition. *Microsiphonales* with a mycelium.
Type genus. *Nocardia* Toni and Trevisan, 1889.
Classification. This family contains 2 genera:

A. Grows aerobically, easy of cultivation, and producing arthrospores. Genus 1, *Nocardia* Toni and Trevisan, 1899.

B. Grows best anaerobically, but can often grow aerobically, difficult of culture, and not producing arthrospores. Genus 2, *Cohni-streptothrix* Pinoy, 1911.

The reader interested in mycology may find further particulars on these fungi in Castellani and Chalmers, "Manual of Tropical Medicine," 3rd edition, pages 1040–1062.

AGRANULAR BRONCHO-NOCARDIASIS

(*Broncho-streptothricosis, Pseudo-actinomycosis, Pseudo-tuberculosis.*)

This is one of the most serious types of *Broncho-mycosis*. It generally runs a chronic course, although occasionally acute cases are met with. The patient loses flesh, becomes

anaemic, often has serotine fever; expectoration is at first muco-purulent, later tinged with blood; true *haemoptysis* may occur. The physical examination of the chest may reveal patches of dullness, crepitations, and pleural rubbing; occasionally, however, the physical examination will reveal nothing at all.

The microscopical and cultural examination of the sputum is most important, segments of thin, bacillary fungi will often be found, branching, at times acid-fast, at times not acid-fast but gram-positive. Aerobic and anaerobic methods of cultivation should be used, as some *nocardias* (*cohnistreptothrix*) grow only anaerobically.

The treatment of these cases consists of giving potassium iodide in large doses internally and autogenous *nocardia*-vaccines by hypodermic injection. Occasionally this mixed treatment gives good results, but in my experience most cases do not answer to this or any other treatment I know of, and end in death.

GRANULAR BRONCHO-NOCARDIASIS

(*Broncho-actinomycosis.*)

The clinical symptoms are very similar to those observed in *Agranular broncho-nocardiasis*, but the sputum contains small granules composed of an enormous number of thin mycelial filaments, mixed with some debris. This type of *nocardiasis* is more amenable to treatment than the agranular type, and potassium iodide in large doses is fairly frequently successful.

ILLUSTRATIVE CASES

(*Agranular broncho-nocardiasis.*)

CASE 1. — European, male, 32 years of age, a planter in various tropical countries during the last 12 years. Two years ago he began complaining of slight cough, with very little expectoration. The physical examination of the chest revealed very little, apart from a slight diminution of resonance in the left supraclavicular region. Cuti reaction negative.

The sputum was examined 12 times for tubercular bacillus with constantly negative results. Instead a branching, gram-positive, partially acid-fast organism was present,

which I succeeded in growing. A protracted course of potassium iodide treatment, combined with the subcutaneous administration of autogenous vaccine, prepared with the fungus, was very successful.

CASE 2. — This is a most interesting case investigated at St. John's Hospital by Dr. Woodward, who has kindly allowed me to quote it and has supplied me with the following notes:

> Captain served through the War, and after demobilization went to Rhodesia where he had previously resided. In the early summer of 1922 he began to feel unwell and showed loss of weight, and had a cough and some expectoration. A few weeks after this, he started to come home on leave to England, and the condition progressed. On his arrival in England he came to see me and told me this history: — He had lost a considerable amount of weight and brought up sputum that at times was blood-stained. He looked very ill, and appeared to be in a condition of rapid *phthisis*. On examining a direct smear of his sputum, I found it full of a network of branching rods, showing numerous ramifications, being acid-fast with Ziehl-Nielsson stain. He had an evening temperature, for some little time, which varied from 100 to 101. Shortly after this he went under the care of a physician, who tried all sorts of treatment of a medicinal nature without its having the slightest effect on the condition.
>
> My findings of the *nocardia* (*streptothrix*) was confirmed in July of last year by Dr. Benians, who inoculated a guinea pig intravenously. The animal showed considerable wasting, and was killed on the 16th day. Multiple nodules were scattered throughout the viscera. In August, 1922, specimens of the sputum were sent to me periodically, always showing the same microscopical picture. Owing to the presence of pyorrhoea in the patient, I was asked to examine his gums. I did not find the *nocardia*, but there were spirochaetes very largely mingled with fusiform bacilli.
>
> The clinical picture showed a steady development, the patient continuing to go gradually down hill.
>
> In November there appeared two pyemic abscesses — one in the neck and the other in the side. I examined the pus from both of these places, and in direct smears they both showed the streptothrix to be present in very large quantities. No other organism was seen, nor was there any growth obtained of any other organism.

He died in the month of November, 1922.

I find that the organism was markedly acid-fast with Ziehl-Nielsson stain, but after keeping, the color tended to disappear. It was gram-positive, and showed distinct variations of staining inside the rods. The organism from the sputum was at first anaerobic, and I grew it in a glucose broth. Later when I obtained the organism from the pus, it was aerobic and anaerobic and grew very much more easily on any media than when I had obtained cultures from the sputum. It showed a white, flowery-looking growth. I gave intra-peritoneal inoculation into a guinea pig and it died on the eighth day.

GRANULAR BRONCHO-NOCARDIASIS

CASE 1. — A Serbian soldier, aged 23, presented all the usual clinical symptoms of pulmonary tuberculosis, great loss of flesh, serotine fever, bloody expectoration. The physical examination of the chest revealed patches of dullness with crepitations and pleural rubbings. The sputum was muco-purulent, occasionally tinged with blood. It contained at times some very small whitish granules the size of a pin-head, composed of an enormous number of thin, mycelial filaments, branching, gram-positive and partly acid-fast. The fungus grew fairly well aerobically on maltose and glucose Agar. The colonies developed slowly, were hard, and firmly attached to the medium. They were of a pinkish color, and gelatine was slowly liquefied. Potassium iodide was administered in large doses and also hypodermic injections of an autogenous *nocardial* vaccine, but without any marked beneficial result.

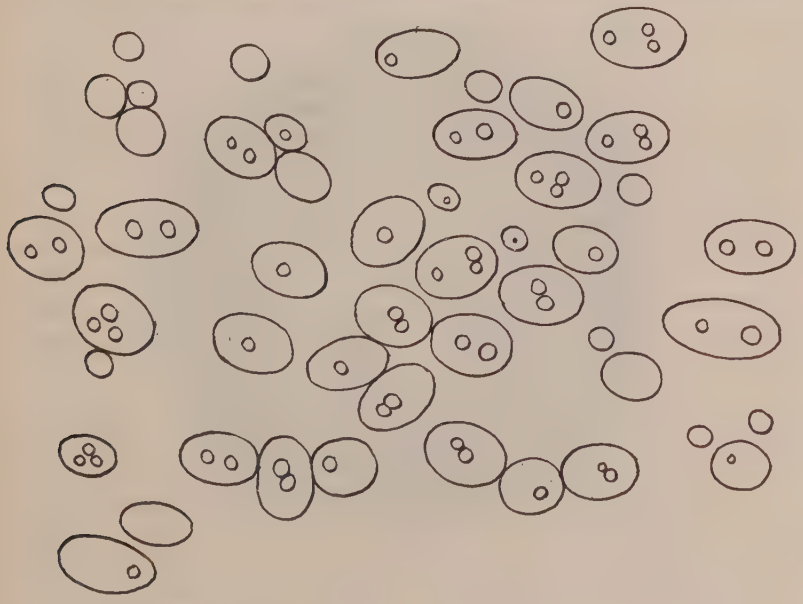
CASE 2. — Young Indian, student, 20 years of age. His medical attendant sent him to me as he suspected tuberculosis, but he could never find the tuberculosis bacillus in the sputum. The patient was very thin and had serotine fever and sweatings; he coughed a great deal; the expectoration was at times muco-purulent, at times haemorrhagic. I had him cough, in my presence, into a sterile Petri-dish, and in the sputum, which was muco-purulent, I noticed several minute, yellowish bodies, or granules, which the microscopical examination revealed as composed of thin mycelial elements, gram-positive, but not acid-fast. I grew the fungus with great difficulty. Potassium iodide in very large doses (gr. xxx. 3 times a day) without any vaccine had an almost

wonderful effect; within 5 weeks all the symptoms disappeared.

BRONCHO-MONILIASIS

I first called attention to this bronchial affection in Ceylon, in 1905, and valuable work on the subject has been carried out recently by a number of authors, Chalmers, O'Connell, Farah, Macfie, Iacono, Taraknath Sur, Thones, Pollacci, Redaelli, Perin, etc. The condition, however, is still little known, though it has been found in many tropical and subtropical countries, and also in temperate zones.

Pinoy has described cases in France, Pijper in South Africa, Macfie in West Africa, and Chalmers and MacDonald and Farah have observed a number of cases in the Soudan and Egypt. Taraknath Sur has made a thorough study of the disease in India. Iacono has found several cases in the south of Italy, and cases have recently been found in England by Douglas, Thompson and myself, and in America by Johns, Boggs and Pincoff and Simon. The condition appears to be caused by several species of the genus *Monilia* Persoon, usually *M. tropicalis* Castellani, *M.* Pinoyi Castellani, *M. krusei* Castellani, and *M. metalondinensis* Castellani.



MONILIA TROPICALIS FROM GLUCOSE-AGAR CULTURE.

As regards the botanical characters of the genus *Monilia*, the original definition by Persoon is "*Stipitata aut effusa byssoidea. Fila Moniliformis articulata.*" These fungi are stated to be characterized by the sporophores being simple or sub-simple, and producing by constriction at their extremities a chain of large lemon-shaped conidia, often provided with a disjunction apparatus. The general tendency at the present time, however, is to extend the term "*monilia*" so as to include all those organisms of the family *Oösporaceae* Saccardo, 1886, the vegetative body of which (Thallus) in its parasitic life (*in situ*, in the lesions) appears as a mass of mycelial threads and free budding forms, some of the mycelial filaments being long and branched, and of rather large size, and often presenting arthrospores. In the saphrophytic life (cultures on the usual solid laboratory media) mostly yeast-like roundish or oval bodies are seen, while mycelial filaments are very scarce, or absent, and when present they are rather short and consist only of a few articles. *Monilia* fungi very often ferment glucose and other carbohydrates with production of gas.

EXPERIMENTAL PULMONARY MONILIASIS. LUNGS OF INOCULATED RABBIT.

For practical purposes *Monilias* may be conveniently classified, according to some of their biochemical characteristics, as follows:

1. Gas produced in glucose only: *Monilia balcanica* Castellani group.
2. Gas produced in glucose and levulose only: *M. krusei* Castellani group.
3. Gas produced in glucose, levulose, and maltose: *M.* Pinoyi Castellani group.
4. Gas produced in glucose, levulose, maltose, and galactose: *M. metalondinensis* Castellani group.
5. Gas produced in glucose, levulose, maltose, and galactose: *M. tropicalis* Castellani group.
6. Gas produced in glucose, levulose, and saccharose: *M. guillermondi* Castellani group.
7. Gas produced in glucose, levulose, galactose, and saccharose and inulin: *M. macedoniensis* Castellani group.
8. Gas produced in dextrin, in addition to other sugars: *M. pseudolondinensis* Castellani group.
9. Gas produced in lactose in addition to other sugars: *M. pseudotropicalis* Castellani group.
10. Absence of gas fermentation in any sugar: *zeylanica* Castellani group.

It must be kept in mind that certain sugar reactions are not constant, and several species of *Monilia* may, after a time, lose their power to ferment some carbohydrates. Hence the determination of some species can be carried out only with strains very recently isolated. It must also be kept in mind that *Monilias* presenting the same biochemical reactions may differ enormously as regards pathogenicity. Some may produce a severe infection when inoculated into rabbits, others may be quite harmless.

Clinically, a mild type and a severe type of the malady may be differentiated, with, of course, a number of intermediate cases. In the *mild type* the general condition of the patient is good and there is no fever. The expectoration is muco-purulent, often scanty, and does not contain blood. The physical examination of the chest is negative or reveals

TABLE SHOWING BIOCHEMICAL CHARACTERS OF COMMON *MONILIAS*

	GLUCOSE	LEVULOSE	MALTOSE	GALACTOSE	SACCHAROSE	LACTOSE	MANNITE	DULCITE	DEXTRIN.	RAFFINOSE	ARABINOSE	ADONITE	INULIN	SORBITE	STARCH	GLYCERINE	INOSITE	SALICINE	AMYGDALIN	ISODULCITE	ERYTHRITE	GELATINE	SERUM	LITMUS MILK	COLOUR OF GROWTH ON GLUCOSE AGAR
Monilia Zeylanica Castellani	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	Yellowish
M. Balcanica Castellani	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	White
M. Parabalcanica Castellani	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	"
M. Krusei Castellani	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Parakrusei Castellani	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	"
M. Pinoyi Castellani	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Nabarroi Castellani	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	"
M. Metalondinensis Castellani	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Alba Castellani	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	"
M. Albicans Robin	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	+	+S	C	"
M. Tropicalis Castellani	G	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Metatropicalis Castellani	G	G	G	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	C	"
M. Rhoi Castellani	G	G	O	G	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Guiller Kondi Castellani	G	G	O	O	G	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	O	O	O	"
M. Macedoniensis Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	C	"
M. Macedoniensoides Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	O	O	O	"
M. Parachalmersi Castellani	G	G	O	G	G	O	O	O	O	O	O	O	G	O	O	O	O	O	O	O	O	+	O	C	"

G = Gas. O = Absence of gas or coagulation. C = Presence of clot. + = Positive. S = Slight.

THREE STRAINS OF MONILIA TROPICALIS CASTELLANI, ISOLATED FROM CASES OF BRONCHOMONILIASIS (GLUCOSE-AGAR CULTURES).

only a few râles. The condition may last for several weeks or months, or get cured spontaneously, or continuing, may turn into the severer type.

The *severe type* closely resembles *phthisis*. The patient becomes emaciated, there is hectic fever, and the expectoration is often haemorrhagic. The physical examination of the chest may show patches of dullness, fine crepitations, pleural rubbing. This type may end fatally.

The treatment consists in giving potassium iodide, with which glycerophosphates and balsamics may be associated. It is interesting to note, however, that in a certain number of cases potassium iodide has practically no beneficial action whatever. Vaccines are occasionally useful.

ILLUSTRATIVE CASES

CASE 1. — A. T. S., male, pensioner, born 1890, joined the British Army in 1914. While serving in Egypt in 1916 noticed slight cough with scanty expectoration, but his general condition of health was fairly good. Ailment continued till December, 1921, when the sputum began to be bloody and the patient began losing flesh. Weight in July, 1919, was 11 stones, 4 pounds; March, 1922, 9 stones, 8 pounds; June, 1922, 8 stones, 13 pounds.

He was suspected to be suffering from tuberculosis and was sent to the Ministry of Pensions Hospital, at Orpington, on March 31, 1922, for observation. His general condition of health was fairly good, but he was very thin. The patient had a slight serotine fever of low type, 99 F. to 99.4, not influenced by quinine. There were no regular sweats. The cough was more severe in the morning than at night. The examination of the chest did not reveal anything very definite. A few coarse râles were present; the X-ray examination did not show any evidence of tubercular lesions. Complement deviation test for tubercular bacillus, negative. Wassermann negative.

The sputum was examined for the tuberculosis bacillus many times — always negative. A fungus was grown with the characteristics of *Monilia metalondinensis* Castellani.

He was treated with potassium iodide and creosote, and all the symptoms disappeared. He was discharged from the hospital as cured, but we kept in touch with his family doctor, who wrote to us some months afterward that the patient was feeling well and was able to do a full day's work.

CASE 2. — Col. A. S., while in India, developed symptoms of subacute bronchitis with muco-purulent expectoration and occasionally haemorrhage. He was diagnosed as a case of *Broncho-moniliasis* and sent home. I was able to confirm the diagnosis. He got well on potassium iodide and creosote. In this case the *monilia* was of the Pinoyi type.

INOCULATION EXPERIMENTS IN THE LOWER ANIMALS

In Ceylon I carried out a fairly large number of researches on the virulence of various *monilias* and the experimental reproduction of *Broncho-moniliasis*. More recently Douglas, Iacono, Redaelli, and others have worked on the subject in England and Italy. The results of these researches may be condensed briefly as follows:

1. A few *monilia* strains are non-virulent. Their inoculation into rabbits and guinea pigs by the subcutaneous, intravenous, intraperitoneal, intrapleural, intrapulmonary route does not kill either the rabbit or the guinea pig, and the inoculated animals do not show any sign of sickness. These strains have generally been isolated from the air.

2. Certain *monilia* strains are virulent and kill the rabbit and guinea pigs, when inoculated intravenously or intrapulmonary, but do not produce any evident pseudo-tubercular nodular condition of the lungs.

3. Certain *monilias* when inoculated intrapulmonary (and at times intravenously) produce a peculiar nodular condition of the lungs. For instance, if ½ or 1 cc. of a thick emulsion of *Monilia metalondinensis* Castellani strain C (isolated from a severe type of *Broncho-moniliasis*) is injected intrapulmonary in a rabbit through the thorax by means of a syringe and the animal is killed 15 to 20 days after, the post-mortem will show that both the lung which was injected and the lung which was not injected present numerous white nodules, which are generally larger in the inoculated lung. Some of these nodules may coalesce, forming a staphyloid mass. The invasion of the non-inoculated lung apparently is by the bronchi, which in many cases can be made out to be greatly expanded and in some places their wall has given way. The histological examination of the smaller nodules, which are about ⅛ inch in diameter, shows that the center is composed of masses of small cells and polymorphonuclear leucocytes. Further out, the cells are fewer in number. This corresponds to the area of the degenerating expanded bronchiole. Still further out there is a ring of endothelial cells; many of them are phagocytic, containing smaller white cells, and there are a few large multi-nucleated giant cells. There are also in this ring a large number of eosinophile cells. At times the

cells in the center of the nodules are markedly degenerated, the nodule becoming caseous. Stained with gram a section shows only a small number of *monilia* and few of the spores take the gram stain. Between the nodules there is no pneumonia in most cases, but there is some congestion and there is a considerable increase of endothelial cells. In the small arteries the intima is greatly thickened. The above histological description is based on the researches carried out on the subject by Douglas, Thompson, and myself. The animal inoculations were performed by Douglas. The histological lesions found in experimental *Moniliasis* have been also thoroughly studied by Redaelli.

Diagnosis. — The diagnosis is based on the absence of the tubercle bacillus and the constant presence of *monilias* in the sputum. It is essential that the sputum should be collected in sterile receptacles after the patient has gargled thoroughly with warm, sterile water and the sputum should be examined immediately. In certain cases the microscopical examination of the sputum shows spore-like, roundish or oval cells often presenting a double contour and occasionally some portions of mycelial threads. In other cases, the microscopical examination is completely negative, and the fungus can be found only by cultural methods. At any rate, it is impossible to make a definite diagnosis of *Bronchomoniliasis* without a cultural investigation, which should be carried out as follows:

A small amount of sputum is smeared on several tubes of glucose or maltose agar, which should be kept at a temperature of 22 to 25 C. for 2 or 3 days, when, in positive cases, white, rather large, roundish colonies will appear, easily differentiated, as a rule, with a little practice, from the colonies of cocci and other bacteria. To determine the species of *Monilia* present, the strain isolated should be further investigated by inoculating milk, gelatine, serum and the following carbohydrates — glucose, levulose, maltose, galactose, saccharose, inulin and dextrin; and animal inoculations in rabbits should also be performed to see whether the strain isolated is virulent or not, and whether it is capable of producing pulmonary lesions.

It is essential to remember that the mere presence of a *monilia* fungus in the sputum should never be considered

sufficient to establish the diagnosis of *Broncho-moniliasis.* When a *monilia* is found in a sputum collected with all due precautions to avoid external contaminations and examined at once, there are 3 possibilities:

1. The *monilia,* though present in the expectoration, is not virulent and not pathogenic, and lives saprophytically in the bronchi. In such an event the *monilia* inoculated intravenously into a rabbit will be found to be non-virulent, and when inoculation is intrapulmonary it will produce no lesions in the lungs and no general infection.

2. The *monilia,* though virulent, may represent only a secondary invader, a secondary infection; in this case the intravenous injection of the fungus will kill the rabbit; the intrapulmonary injection will not cause any localized nodular affection in the lungs, — it will induce a general fungus septicemia from which the animal will die.

3. The *monilia* is the real cause of the broncho-alveolar condition; in such cases the intrapulmonary injection into a rabbit will produce a very characteristic nodular condition of the lungs. When the animal dies spontaneously or is killed, 15 to 21 days after the intrapulmonary injection, both lungs (the one injected and the other in which no injection was made) are found to be studded with a large number of white nodules, containing the fungus. These white nodules are about $\frac{1}{8}$ of an inch in diameter. In the intervening lung tissue there are signs of congestion, but no pneumonia.

The center of the small nodules is composed of masses of small cells, polymorph leucocytes, — further out there is a ring of endothelial cells, many of them phagocytic and containing smaller white cells; and there are a few large *multinucleated giant cells* and a large number of eosinophile cells. The cells in the center of the nodule are markedly degenerated and the nodule is becoming caseous. Sections stained by gram show only a small number of monilias, and few of the spores take the gram stain. Between the nodules there is some congestion but no pneumonia, and there is a considerable increase of endothelial cells. In the small arteries the intima is greatly thickened. The invasion of the lung tissues (in the side not injected) apparently takes place through the bronchi. These can in many cases be made out to be greatly expanded, and in some places their wall has given way.

PRIMARY AND SECONDARY BRONCHO-MONILIASIS

Primary *Broncho-moniliasis* should be distinguished from secondary *Broncho-moniliasis*, which fairly frequently develops in cases of tuberculosis and other chronic conditions, as shown by Chalmers, Macfie and Ingram, myself, and other observers. A diagnosis of primary *Broncho-moniliasis* should be arrived at by using great caution, because: —

First, *monilia* fungi are frequently very abundant in the air of tropical countries, and very quickly contaminate samples of sputa that by any chance have been exposed to the air, even for a few seconds.

Secondly, these fungi, especially in the Tropics, are not rare in the mouth, in the saliva, and therefore a patient should be made to gargle and rinse his mouth with sterile salt solution before he is asked to cough and expectorate.

Thirdly, even if the fungus be present in the mucus originating from the bronchi, there are apparently certain cases in which the fungus is not pathogenic, being merely a saprophytic organism.

A definite diagnosis of primary *Broncho-moniliasis*, therefore, should be arrived at with great caution, when the bronchial expectoration collected with every precaution and examined at once contains a *monilia*, tubercle bacilli being absent, and the amount of the fungus present decreases rapidly with the gradual improvement of the condition. Pathogenic *monilias* mostly belong to the following groups:— *krusei, metalondinensis, Pinoyi, tropicalis.* The *monilia*, as I have already stated, not only must be virulent to the rabbit by intravenous inoculation, but the intrapulmonary injections of it must induce in the rabbit lungs a nodular condition which later becomes caseous.

Mixed infections. — Cases of apparently true mixed infection, as, for instance, *Broncho-moniliasis* and *Broncho-spirochaetosis* have been put on record by several observers.

Prognosis. — The prognosis of true primary *Broncho-moniliasis* must be reserved, as at times no treatment is of any avail, and the patient goes from bad to worse and finally dies.

Treatment. — Potassium iodide is useful in certain cases, but not in all. It is advisable to associate with it the admin-

istration of balsamics (principally creosote) and glycerophosphates. *Monilia* vaccines are useful in only a few cases.

TEA-TASTER'S COUGH

In connection with *Broncho-moniliasis*, I might say a few words on the so-called "*tea-taster's cough*" and "*tea-factory cough.*" In 1906 a young assistant in one of the big Ceylon firms, a tea-taster, came to consult me about a chronic cough, which he said had not yielded to ordinary treatment, and had been suspected by several medical men to be of tuberculous origin. He emphatically stated, however, that he did not believe it was tuberculosis. "I am merely suffering," he said, "from tea-taster's cough," an expression I had never heard before. The general condition of the patient was good, and the physical examination of the chest revealed only a few coarse râles. The microscopical examination of the sputum was negative for T.B.; instead, I noticed microscopically some mycelial filaments and some yeast-like bodies. I inoculated several glucose-agar tubes, and I grew a *monilia* fungus which, at the time, I believed to be an endomyces.

How did this patient get infected? Tea-tasters, in order to judge of the quality of the various teas, not only taste infusions, but often fill their hands with the tea-leaves and bury their noses in them, sniffing them up; in this way a certain amount of tea-dust enters the nasal cavities.

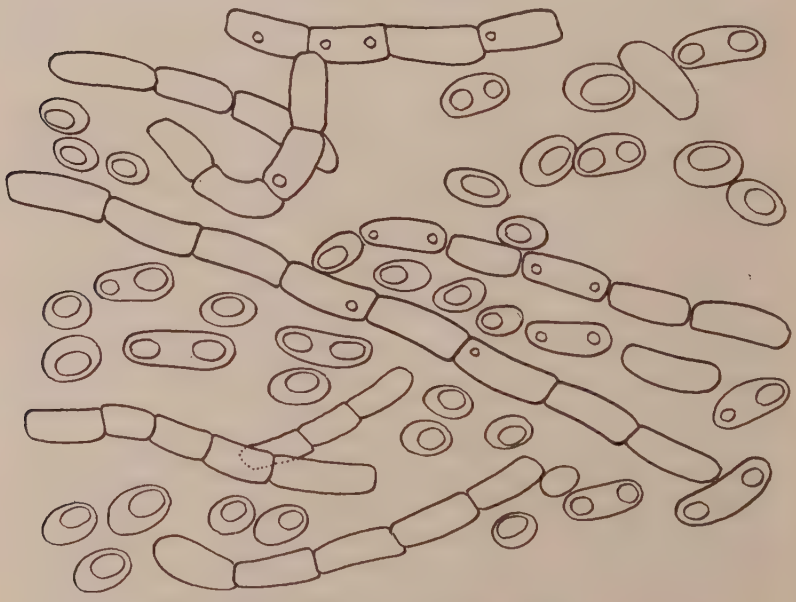
Now if one examines tea-dust, in Ceylon, one finds that it contains fungi of the genus *Monilia* constantly, of the genera *Aspergillus* and *Penicillium* frequently, and of the genus *Oidium* occasionally. A peculiar streptococcus is also very often present. The same organisms are not rarely found in the nasal cavities of tea-tasters, and when bronchial symptoms appear in them, *monilia*-like fungi are present in the expectoration. It is probable, therefore, that the so-called tea-taster's cough is a *Moniliasis*, especially as a guinea-pig, in the nostrils of which I insufflated tea-dust regularly, died with symptoms of chronic broncho-pneumonia.

What I have said about "tea-taster's cough" applies to a great extent to the so-called *tea-factory cough.* For many years planters have noted, in Ceylon, that the coolies doing work in the tea-factories, where the leaves are dried and there

is a large amount of tea-dust floating about, after some months become weak, lose flesh, and often have a cough with muco-purulent expectoration. The planters have found by experience that these coolies must be taken away from the factory and sent to work in the field, and then the symptoms slowly disappear. I have examined some of these coolies, and their expectoration practically always contains fungi of the genus *Monilia*. I have little doubt, therefore, that the so-called "tea-factory cough" is a *Broncho-mycosis*, and probably a *Broncho-moniliasis*.

BRONCHO-OIDIOSIS

This is clinically identical to *Broncho-moniliasis* and, as is the case with *Broncho-moniliasis*, a primary and a secondary form should be distinguished. The fungi belong to the genus *Oidium sensu* Pinoy and are characterized by abundant mycelium with numerous arthrospores but, in contrast to



OIDIUM ROTUNDATUM FROM CULTURE.

Monilia, free yeast-like budding cells are absent or rare. They may produce acidity in various sugars and other carbo-

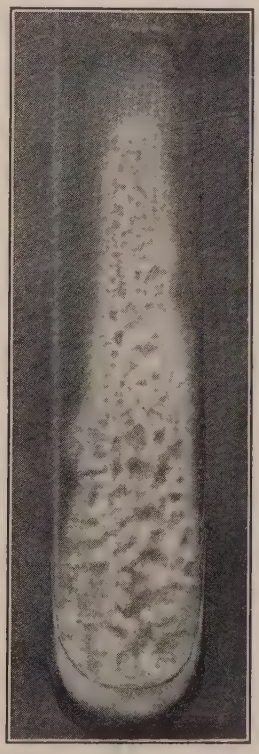
hydrates, but never gas. This genus (*sensu* Pinoy) contains 4 principal species:

O. Lactis Link, 1809.
O. Rotundatum Castellani, 1911.
O. Asteroides Castellani, 1914.
O. Matalense Castellani, 1915.

They may be differentiated as follows:

1. Surface of the culture smooth or only very slightly crinkled, produces acidity in glucose, though not constantly, but in no other carbohydrate. *O. Lactis.*
2. Surface with *duvet*, produces no acidity or only very slight in the usual carbohydrates. *O. Matalense.*
3. Surface vermiform, acidity in glucose, levulose, galactose, maltose and lactose. *O. Rotundatum.*
4. Colonies with peculiar radiating appearance. *O. Asteroides.*

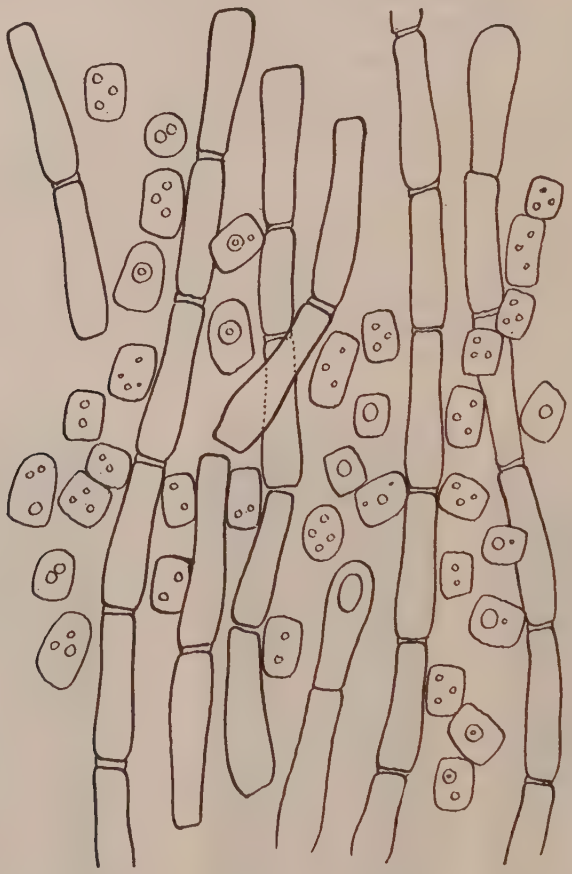
OIDIUM ROTUNDATUM, CASTELLANI.



OIDIUM ASTEROIDES, CASTELLANI.

OIDIUM MATALENSE, CASTELLANI.

The reader interested in mycology may find further details regarding these fungi in Castellani and Chalmers' "Manual of Tropical Medicine," 3rd edition, page 1093.



OIDIUM ASTEROIDES, FROM CULTURE.

BRONCHO-CRYPTOCOCCOSIS

Symptoms identical with those found in *Broncho-moniliasis*, but the causative fungi found belong to the genus *Cryptococcus*. These fungi consist of numerous yeast-like, budding cells with no mycelium; cultures never present asci, — this is the only characteristic that differentiates them from true Saccharomyces. There are a primary and a secondary type

of *Broncho-cryptococcosis.* The treatment is the same as for *Broncho-moniliasis.*

BRONCHO-ENDOMYCOSIS

This is caused by fungi morphologically identical with *Monilia,* but old cultures show presence of asci. It is a rare condition. The symptoms and the treatment are the same as for *Broncho-moniliasis.*

BRONCHO-SACCHAROMYCETOSIS

This condition is caused by fungi of the genus *Saccharomyces* and other genera of the family of *Saccharomyceteae.* These fungi are characterized from a practical point of view by the following features:

1. Reproduction by budding.
2. Absence of mycelium.
3. Presence of asci in old cultures.
4. Gas fermentation of one or more sugars.

Symptomatology and treatment as in *Broncho-moniliasis.*

BRONCHO-WILLIASIS

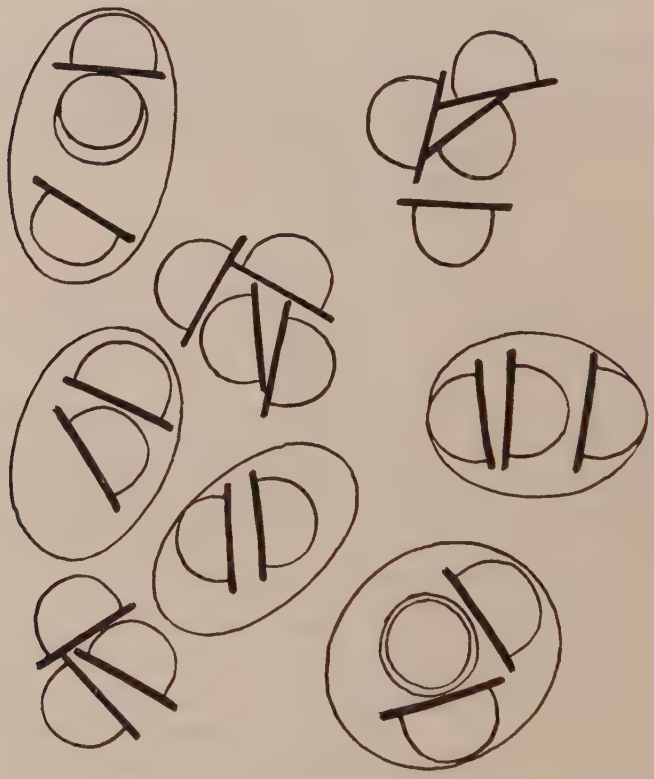
This is a very rare type of *Broncho-mycosis.* The fungi found belong to the genus *Willia.* They are characterized by the peculiarly shaped ascospores, bowler-hat-like, etc. I have had one such case. The patient, a retired planter, got well on potassium iodide. The symptoms were the same as those found in chronic *Broncho-moniliasis.*

BRONCHO-HEMISPOROSIS

This condition, first described in 1910 by me, in Ceylon, is due to fungi of the genus *Hemispora* Vuillemin, which are characterized by the conidiophores terminating in an ampulliform structure with formation of Protoconidia and Deuteroconidia. The species which have so far been isolated in Europe are 2, one identical to *H. rugosa* Castellani, previously found in the Tropics, and the other probably a new species or at least variety: *Hemispora pararugosa* Castellani, Douglas and Thompson. The principal characters of these 2 fungi are, briefly, the following: —

Hemispora rugosa Castellani, 1910 (Syn. *Monilia rugosa* Castellani, 1910), is a hyphomycete with the botanical char-

acters of the genus *Hemispora;* is gram-positive but not acid-fast; the growth on glucose agar is abundant with a crinkled surface, occasionally ceribriform, and amber-yellow or brownish color. No gas is produced in any sugar, but a little acidity may be present in glucose, levulose, saccharose, and maltose. The fungus usually has no action on milk, but occasionally it induces a slight degree of peptonization

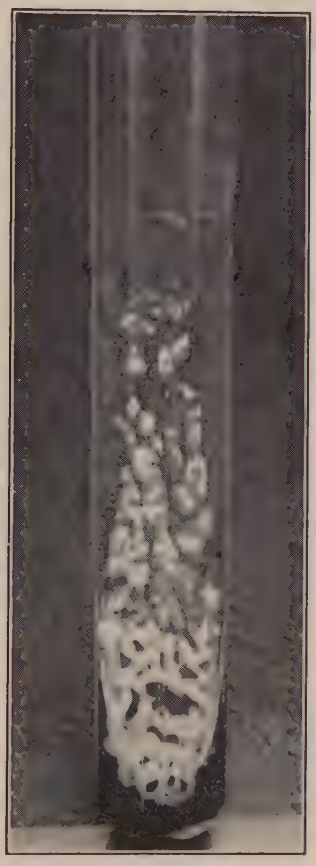


WILLIA ANOMALA, HAUCEN ASCOSPORES.

with a small coagulum at the bottom of the tube. Gelatine is very slowly liquefied. This fungus was first found by me in cases of bronchitis and tonsillitis, in Ceylon, and later by Pijper in certain cases of thrush. I at first placed the fungus temporarily in the genus *Monilia*, later removing it, at the suggestion of Professor Pinoy, to the genus *Hemispora.*

Hemispora pararugosa Castellani, Douglas and Thompson, 1921, is morphologically and culturally very similar to *H. rugosa*. It is gram-positive, but not acid-fast. It does not produce gas or acid in the usual sugars and carbohydrates, but at times produces acidity in starch. It does not liquefy gelatine, and there is no production of acid or clot in milk.

HEMISPORA RUGOSA, CASTELLANI.
(GLUCOSE-AGAR CULTURE.)

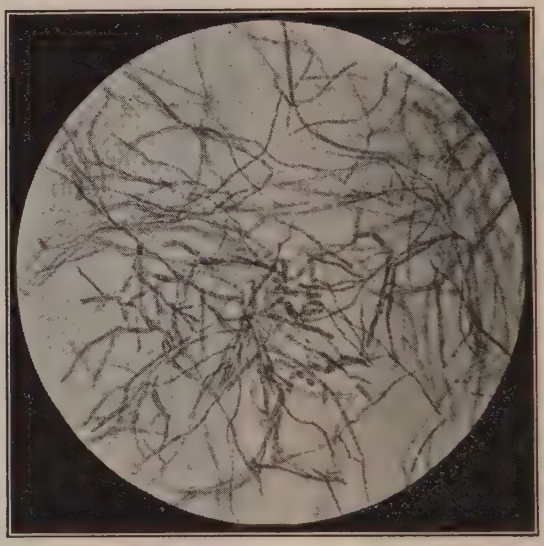


HEMISPORA RUGOSA, CASTELLANI.
(GLUCOSE-AGAR CULTURE.)

Symptomatology. — A mild and a severe type of the affection can be distinguished. In the mild type the general condition of the patient is good, there is no fever, and he simply complains of cough. The expectoration is muco-

purulent, and does not contain blood. The physical examination of the chest is negative, or only reveals a few coarse râles.

The severe type closely resembles *phthisis;* the patient becomes emaciated, there is hectic fever, and the expectoration may be bloody. The physical examination may reveal patches of dullness, fine crepitation and pleural rubbing. It is interesting to note that the affection occasionally devel-



HEMISPORA PARARUGOSA, CASTELLANI, DOUGLAS AND THOMPSON.

ops after a tonsillitis caused by the same fungus, and characterized by the presence of yellowish or greyish patches.

Treatment. — Potassium iodide in large doses generally answers well.

BRONCHO-ANAEROMYCOSIS

This *mycosis* has been investigated by Douglas, Thompson and myself. We have given, temporarily, the generic name *Anaeromyces* to a group of bacillary fungi of the order *Microsiphonales* Vuillemin, 1912, which are found in certain cases of bronchitis, and which show transition and intermediate characters between the genus *Corynebacterium* Lehmann and Neumann, 1896, the genus *Mycobacterium* Lehmann and

Neumann, 1896, and the genus *Nocardia* Toni and Trevisan, 1889 (*Cohnistreptothrix* Pinoy 1911, *pro-parte*), of the family *Nocardiaceae* Castellani and Chalmers 1918 (*Actinomyces* Lavhner-Sandonal, *Trichomycetes* Petrusky).

The organisms of this group, *Anaeromyces*, are very closely related to the genus *Corynebacterium* Lehmann and Neumann (Diphtheria and diphtheroid bacilli) and the genus *Nocardia* Toni and Trevisan (*Actinomyces* Harz, *Discomyces* Rivolta, *Streptothrix* Rossi-Doria, *Oöspora* Sauvageau and Radias, *Cohnistreptothrix* Pinoy, *pro-parte*), but, in contrast to the former, branching is much more marked, and they are strictly anaerobic; and, in contrast to the latter, the mycelium is very much less developed, the growth is moist and not dry and crinkled, and they never give rise to actinomitic granules in the lesions. They are gram-positive, non-motile, and not acid-fast. These germs or similar cones, were found in cases of bronchitis in 1904 by Chalmers and myself, and were referred to in a short paper read at the time as "Bronchial Anaerobic Diphtheroid Bacilli," but the observation attracted very little notice. They are also somewhat similar to *Bacillus Vitulorum* Flugge.

Anaeromyces bronchitica Castellani, Douglas and Thompson — *Morphological and Staining Characteristics.* — The organism is bacillus-like and resembles in its shape a diphtheroid bacillus, but branching is much more marked. It is gram-positive and not acid-fast. It measures 3 to 5 microns in length, and 0.3 micron in breadth.

Motility. — The organism is non-motile.

Relation to oxygen. — The organism is an obligate anaerobe.

Cultural characters. — Provided a strictly anaerobic technic be used, the germ grows well in many of the usual laboratory media. The growth on glucose agar and other media is not very characteristic. The fungus does not seem to grow in gelatine at 22 degrees C.

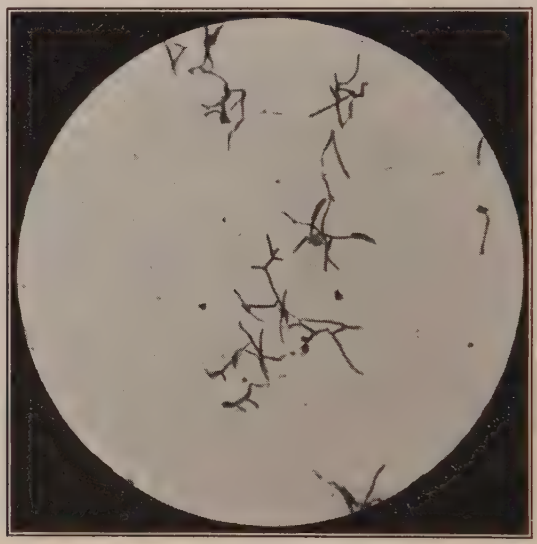
Biochemical reactions. — There is no formation of acidity or gas in any carbohydrate we have experimented with, viz., glucose, levulose, maltose, galactose, saccharose, lactose, and inulin.

Animal experiments. — The action of this organism in the lower animals has not been fully investigated, but it does not seem to be pathogenic to guinea pigs, rabbits or mice.

Pathological conditions in man in which Anaeromyces bronchitica has been found. — The fungus has been isolated from a fairly large number of cases of bronchitis which may be classified into two groups: —

The Haemorrhagic type.
The Muco-purulent type.

Cases of the haemorrhagic type closely resemble pulmonary tuberculosis; there may be intermittent or remittent



ANAEROMYCES BRONCHITICA, CASTELLANI, DOUGLAS AND THOMPSON

fever; the patient may become anaemic and lose flesh; the expectoration contains blood and is at times of very characteristic bright brick-red color. The physical examination of the chest may be at times almost completely negative; at other times it may show signs, such as patches of dullness and crepitations, pointing to tuberculosis.

The symptoms noted in the muco-purulent type do not differ from those of an ordinary case of subacute or chronic bronchitis. The sputum is muco-purulent, or at times purulent; there may be slight fever, but the general condition of the patient is not affected for a long time. In some cases the muco-purulent type, after a variable period of time, turns into the haemorrhagic type.

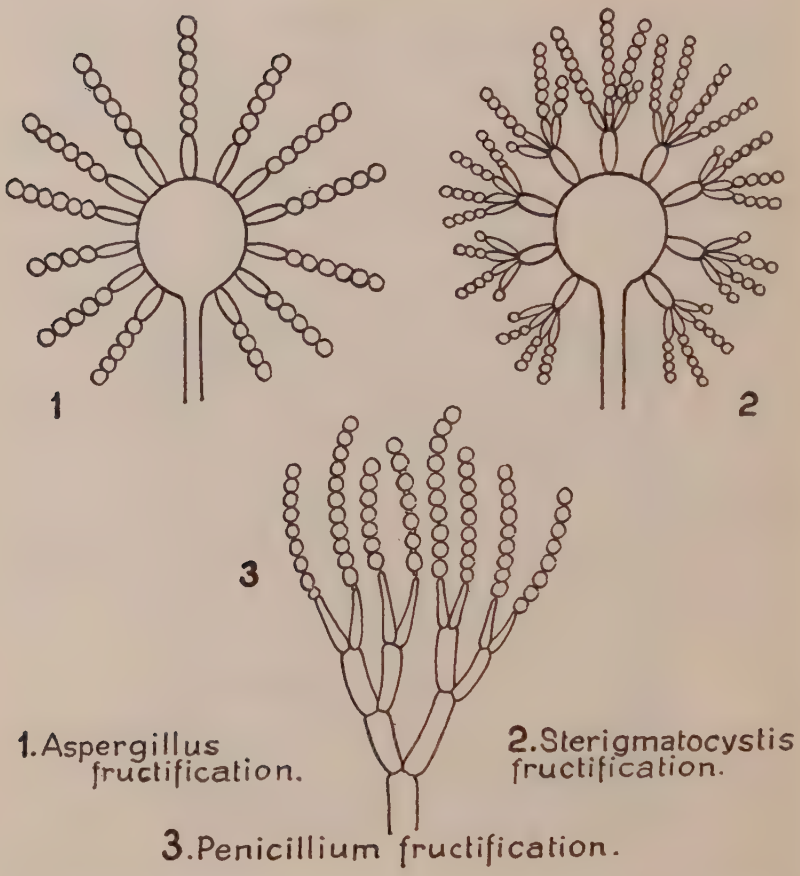
Geographical distribution. — The organism has been found in cases which contracted the disease in Ceylon, in the Federated Malay States, Serbia, Italy, France, and England.

Mixed infections. — The organism has been grown occasionally from bronchial cases in which *monilia* and other fungi, and also the tubercle bacillus, were present.

Pathogenicity of Anaeromyces. — The animal experiments carried out by Douglas do not seem to show that the germ causes any very serious lesion in guinea-pigs, rabbits, or mice, and this is, of course, an argument against the organism's being pathogenic. On the other hand, the following facts are in favor of its pathogenicity to man: (1) The anaeromyces present in the sputum rapidly decrease in amount, and finally disappear with the gradual improvement of the bronchial condition; and (2) in a number of cases the haemorrhagic expectoration very rapidly ceases and all the symptoms quickly disappear, when an anaeromyces vaccine is used without any other treatment. It is therefore probable that anaeromyces has at least some part in the aetiology of certain cases of haemorrhagic bronchitis.

BRONCHIAL-ASPERGILLOSIS

This affection, known also as *Broncho-aspergillomycosis*, pseudo-tuberculosis, *Aspergillus pneumomycosis*, and in France, *Maladie des gaveurs des pigeons* (pigeon-breeders), is caused by fungi of the genus *Aspergillus* Micheli *and Sterigmatocystis* Cramer. These fungi are easily recognized by their very characteristic fructifications: the conidiophore terminates into an ovoid or roundish formation, from which take origin numerous elongated claveiform elements, each of which supports a chain of roundish conidia. These fungi are generally saprophytes but occasionally become true parasites. They grow quite easily in both acid and alkaline media. It is interesting to note that iron and manganese have a favorable influence on their growth and sporulation. When growing parasitically in the tissues of man and animals, they often lose some of their characters and the typical fructifications are often absent, only mycelial segments and yeast-like cells being seen.



The classification of *Aspergillus* is difficult. In practice the principal types may be differentiated as follows:

1. *Conidia*, of very large size (9 to 15 microns in diameter), yellow, or reddish-yellow, or gold-brown. *A. herbarorum* Wiggiers.
2. Similar to *herbarorum* in general characteristics, yellow or yellowish-green, but *conidia* somewhat smaller though still large (7 to 8 microns). *A. repens* De Barry.
3. Similar to above two, as regards color and being yellow or greenish-yellow, but spores smaller (5 to 7 microns in diameter) and with a granular surface. *A. flavus* De Barry.

4. On solid media, *brownish-black* if the medium is alkaline or neutral, *greenish* if the medium is acid; *conidia* small (2 to 3 microns) and smooth. *A. fumigatus* Fresenies 1775.

Symptomatology. — There are signs of muco-purulent bronchitis. In severe cases haemoptysis may occur and there may be serotine fever. The disease often terminates fatally, and at the post-mortem numerous mycotic nodules may be found in the lungs and occasionally in the liver and kidneys and other organs. Care should be taken to distinguish secondary *Aspergillosis* from primary *Aspergillosis*. Secondary *Aspergillosis* occasionally develops into tuberculosis, and not very rarely in gangrene of the lungs.

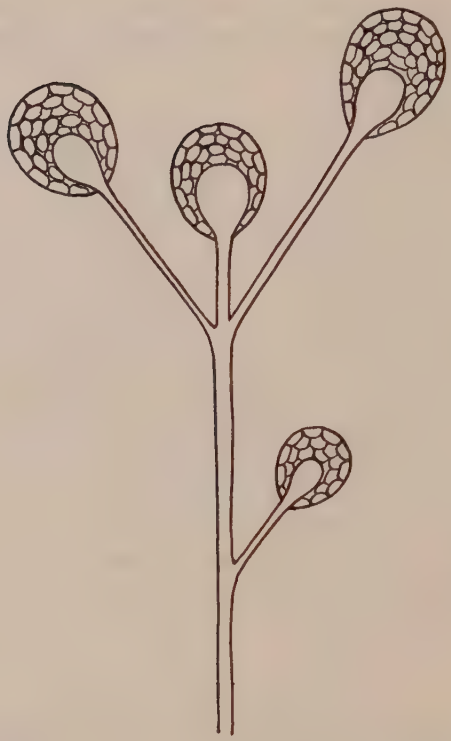
Diagnosis. — This is based on the mycological investigation of the sputum. It is important to note that, as a rule, in the sputum only conidial elements and mycelial elements are seen microscopically.

Treatment. — This is difficult. Potassium iodide is useful in incipient cases, and a change of climate and occupation should be recommended.

BRONCHO-PENICILLIOSIS

The condition is clinically identical to *Broncho-aspergillosis*, but the causative fungi belong to the genus *Penicillium* Link. Fungi of this genus are characterized by their fructifications, the whole fruit-bearing hypha with its *sterigmata* and *conidia* resembling a hair-pencil (*Penicillium* — Hair pencil). The species most frequently found in man is *P. crustaceum* Linnacus (synonyms *P. glauccum* Linnacus, *Monilia digitata* Persoon). It is often found living *saprophytically* on bread, cheese, and fruits. The *conidia* are spherical, smooth, of a maximum diameter of 4 microns.

In Macedonia, during the World War, a Serbian soldier was sent to the hospital to which I was attached, with the diagnosis of pulmonary tuberculosis. He had been wasting for two months, and had serotine fever. Expectoration muco-purulent, at times bloody. Repeated examination for T.B. *negative.* A few mycelial threads present. A fungus was grown with the characters of a *Penicillium*, probably *P. crustatum.* Potassium iodide in full doses acted well.



RHIZOMUCOR PARASITICUS LUCET AND COSTANTIN.

BRONCHO-MUCORMYCOSIS

This term is used to designate bronchial and broncho-alveolar affections associated with fungi of the genus *Mucor* Micheli, 1729, and the following genera:—

Lichtheinia Vuillemin, 1904.
Rhizomucor Lucet and Costantin.
Rhizopus, Ehrenberg.

These genera belong to the family *Mucoraccae*, the members of which are characterized principally by the following features: aerial hyphae are present (*gomidiophores*), each of which supports on its distal extremity a pear-shaped globular or claviform formation, the *sporangium* or *gonidiangium* which is at first separated from the gonidiophore by a *septum*. The septum later protrudes into the lower part of the *sporangium* to form a variously-shaped structure called *columella*.

Inside the *sporangium*, *gonidia* (Endospores) develop by free cell formation. Part of the sporangial protoplasm not used in the formation of the endospores becomes transformed into a peculiar mucilaginous substance, which, at a later period, becoming swollen by absorption of water, causes the bursting of the *sporangium*. Each endospore or *gonidium* which has become free in this way gives rise to a mycelial tube by germination. The mycelial tubes ramify, and an abundant mycelium is produced.

In some species a form of partial sexual reproduction takes place by a process of zygosporosis, or conjugation of two gametes which morphologically are not of different shape or structure, — that is to say, they are not sexually differentiated. It must be noted that many species, when growing in unfavorable media, reproduce only by *conidia*. They require plenty of oxygen, and therefore the media tubes must never be closed with rubber caps; otherwise they lose their characteristic and grow *monilia*-like or yeast-like. The family *Mucorraceae* may, from a practical point of view, be classified as follows:

1. *Mycelium* ramified, no rhyzoids	(root-like hairs by which the plant is attached to the medium) *Mucor*, Micheli, 1729
2. *Mycelium* non-ramified, with or without *rhyzoids*, *sporangium* terminates in a special formation, encircling the base of the columella.	*Lichtheimia*, Vuillemin, 1904
3. *Mycelium* provided with rhyzoids *columella ovoid*	*Rhyzomucor*, Lucet, Costantin, 1900
4. *Mycelium* provided with rhyzoids columella, hemispheric, mushroom-like.	*Rhizopus* Ehrenberg, 1820

For further particulars on the botanical classification of these fungi, the reader may consult Castellani and Chalmers'

"Manual of Tropical Medicine," 3rd edition, pages 972–977.

Illustrative case. — During the World War, while I was in the Balkans, in 1917, a Serbian soldier was sent to me with the diagnosis of pulmonary tuberculosis. He was losing flesh rapidly and felt very weak. Slight fever at night, a fair amount of expectoration, generally muco-purulent. The physical examination of the chest revealed nothing except a few coarse râles. Microscopical examination of sputum for T. B. constantly negative; instead, a few segments of *mycelium* were noticed on several occasions, glucose-agar tubes and other media were inoculated, and a fungus was isolated which at first showed the characters of a *monilia;* in sub-cultures, however, the characteristic features of a mucor appeared with presence of the globular sporangia (*columella*) 5 microns in diameter of yellowish color, spores elliptical smooth. In what way did this man get infected? He was in charge of horses and often had to remove the horse dung, and as is well known horse dung almost always contains *mucor.*

BRONCHO-ACREMONIELLASIS

In a case at first considered to be a *Broncho-aspergillosis* Perin isolated a fungus which was investigated by Pollacci. In glucose-agar it produces a growth which is at first whitish, but later soon becomes black. The microscopical examination of the cultures shows abundant septate mycelium, the hyphae being 3.5–4 microns in breadth. Each conidiosphore bears a terminal round spore 7.7. to 9.7 μ. in diameter, of a dark-brown color. Pollacci considers the fungus to belong to the genus *Acremoniella* and has called it *Acremoniella* Perini. *Broncho-acremoniellasis* clinically is identical with *Broncho-aspergillosis.*

BRONCHO-CLADOSPORIOSIS

From a case of chronic bronchitis with occasionally haemorrhagic sputum I have isolated a fungus very similar to *Chlorosporium* Mansoni Castellani which is the cause of *Tinea nigra.* Potassium iodide answered well.

BRONCHO-ACOLADIOSIS

From two cases of chronic haemorrhagic bronchitis I have isolated a fungus which does not seem to differ in any impor-

tant point from *Acladium* Castellani Pinoy, which is the cause of a peculiar ulcerative condition of the skin. The two cases got well on potassium iodide.

BRONCHO-SPOROTHRICOSIS

In cases of dermal *sporothricosis* the fungus may occasionally attack the bronchi and the pulmonary tissues. But there is also, though it is rare, a primary *Broncho-sporothricosis*. The patient has the symptoms of severe bronchitis or broncho-pneumonia, with muco-purulent expectoration, occasionally tinged with blood. The diagnosis is based on the microscopical and cultural examination of the sputum. The microscopical examination will show presence of yeast-like bodies in certain cases, in others it will be completely negative. The sputum should be inoculated into several tubes of maltose-agar, and left at a temperature of the room for several days. In positive cases whitish colonies generally appear, which soon coalesce, forming a whitish cerebriform mass and this later on becomes black or brownish. For the determination of species, hanging-drop cultures must be prepared, and also cultures on various media, etc. The classification is based principally on the size and shape of the *conidia*, and may be found in the chapters on fungi in Castellani and Chalmers' "Manual of Tropical Medicine."

The prognosis is quite favorable, provided a correct diagnosis is made at an early stage. Potassium iodide in large doses is a specific.

BRONCHO-MYCOSES DUE TO UNCLASSIFIED FUNGI

In Ceylon and in the Balkans, and recently in England, I have come across cases of haemorrhagic bronchitis from which I have isolated some peculiar fungi that have not yet been classed. Potassium iodide answered well in most of them.

CONCLUSION

In conclusion, it would seem to me that the subject of haemorrhagic bronchitis of protozoal, helmenthic and fungal origin deserves to attract more attention than has been the case hitherto. It should be remembered that the subject is

of practical importance; all these conditions I have mentioned are generally mistaken for tuberculosis, but, while pulmonary tuberculosis in the haemorrhagic stage is often incurable, most of the conditions I have described, provided the correct diagnosis is made, in time, are amenable to treatment.

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DISCUSSION.

Dr. F. M. Johns (Opening the Discussion). — It is a rare treat to be allowed to hear of Dr. Castellani's lifetime work in such a few words. Comment and discussion are practically out of the question in the presence of such a master. It is a sad commentary on the diagnostic laboratory-methods of our country, at least, to listen to the description of various infections that may take place in the lungs and bronchial tubes, and to realize that the majority of our sputum-examinations are limited to the search for tubercle bacilli only.

Any one who has lived with Castellani in his books — day and night — cannot fail to appreciate the fact that there must be an

enormous incidence of mycotic infection of the bronchial tubes. The few cases I have had the pleasure of seeing, have all been extremely acute, and some of them have progressed until death; and they have certainly opened my eyes to the severity that some of these infections can achieve. It is very easy to surmise that if you have a limited number of cases in which the mycotic infection is unquestioned, the actual incidence of such cases must be larger still.

I think the trend of thought in North America is slowly changing. At the present time, the X-ray diagnosis of tuberculosis is accepted practically without question — often in the absence of clinical findings, even. One of my cases of pulmonary *blastomycosis* was "positively" diagnosed as tuberculosis by one of our most prominent X-ray specialists. Several of the cases of pulmonary *moniliasis* that I recently reported in the *New Orleans Medical and Surgical Journal* were likewise at first mis-diagnosed on the basis of Roentgen shadows, instead of being diagnosed on direct evidence to be found in the sputum itself.

Dr. Juan Iturbe. — I shall take advantage of this occasion to refer to the *Paragonimus westermani* or *Distomum pulmonale*, called to our attention by Dr. Castellani as one of the causes of the *hemoptysis* of parasitic origin. The *paragonimiasis* has not only been considered in the Old World but also in our new continent. In the United States this parasite has been found in hogs and dogs by Ward, Payne and Kellicott. In South America, Arce in 1916 was able to demonstrate the presence of the characteristic ova in the sputum of various subjects working on the farms in the outskirts of Lima, Peru; and recently in Ecuador several authentic cases of this disease have been described. So far as Venezuela is concerned, we have no observations indicating that these parasites have been found in man.

My investigations demonstrated without possibility of error the existence of the adult trematode in the lungs of several dogs in the Valley of Caracas. While we were studying the fresh-water fauna of the creeks of Caracas, we found in the liver of the snail *Ampullaria luitostoma* a *xiphydiocercaria* which grows in the rediae, averaging in size from 90 to 110 microns, and which, according to its anatomical characteristics, corresponded to the larvae of the *P. westermani* described by Nakagawa. The result of my experiments were published in a monograph entitled "Les Cercaires de la Valleè de Caracas," 1918 — 1 partie, Caracas.

In order to make certain of the life cycle of these parasites we placed in an aquarium several specimens of the mollusk already mentioned, and several specimens of fresh-water crabs collected in

the creeks of the Valley of Caracas or on the neighboring lands. In the aquarium a number of stones were placed and a thin film of sand in order to regulate the natural *modus vivendi* of these animals. Furthermore, we took the precaution to throw into the aquarium livers of the *ampullariae* which contained great quantities of *cercariae* having the characteristic buccal orifice of the larvae of the *P. westermani*. The crabs were carefully examined and at the end of from 2 to 3 weeks we were able to observe in their gills the typical cysts. We were able with these infected crabs to produce serious infections in dogs and rabbits, and to demonstrate the presence of the parasites in the peritoneum, lungs, and pleural cavities.

This disease does not exist in men, in Venezuela, because the inhabitants do not eat raw crabs as they commonly do in Japan and Formosa. The second intermediary host of the *P. westermani* in Venezuela was classified by Miss Rathbun, of the Smithsonian Institution, as a new species called *Pseudotellphusa Iturbei Rathbun* (1918).

In conclusion, — the life cycle of this parasite in Venezuela takes place in the following manner:

1. Host — snail: *Ampullaria luitostoma.*
2. Host — crab: *Pseudotellphusa Iturbei.*

According to our data, the natural infection in crabs is very much reduced; we were able to prove their presence in the cystic form only in the proportion of 1 in 250.

Col. Bailey K. Ashford. — I am not going to say much on Dr. Castellani's admirable paper — for lack of time — but wish to offer a case which convinced me, beyond any question, of the importance of *Broncho-moniliasis.* The patient was a personal friend of mine. He was a very well-educated man, from Boston, in excellent physical condition, and had lived for a long time in the Tropics. One day he came to me with great hilarity, stating that some doctor had accused him of having hookworm. He said, "I am going to let you see my feces, fully expecting that you will also find *monilias.*" I laughed and said, "I will take you up — you have no *monilia.*" But he did have it. The culture from his feces was positive for *M. psilosis.*

He was relieved of 4 or 5 ankylostomas and was at peace with himself until some time afterward I was unexpectedly called to the hospital to see him. He was a man weighing about 160 pounds, in health. When I reached the hospital I saw that he was far gone in sprue, and it was so typical it was unnecessary to go over him. He weighed then about 100 pounds. But he had not come to the hospital for his sprue — he had come for an acute condition of the

lung. The diagnosis was "abscess of the lung." He was operated upon. A culture was taken from the pus. It turned out to be almost a pure culture of *monilia* which I have called "*psilosis.*" Under diet his intestinal condition became better, but was not cured. The fistula remained and caused him great trouble. Fully 3 months went on with his discharging fistula and finally I persuaded him to accept *monilia* vaccines of this type. He was rapidly cured by these vaccines and is now of about normal weight. I mention this case because there was no question whatsoever about the predominating organism. I could also mention many other cases which were apparently tubercular, but which cleared up following treatment of their sprue and the use of *monilia* vaccines.

Dr. A. A. Facio. — In 1922, while we were looking for other micro-organisms in the sanguinolent sputum of various cases which had been primarily diagnosed as, or rather suspected to have been suffering from, tuberculosis or pneumonia, we found the *Spirochaeta bronchialis* in the sputum. The point which at the time interested us most in connection with these cases, was the treatment. We had learned of the good results that had been obtained in the treatment of these cases with neo-salvarsan, and as the condition of the patients had not improved with the treatment which had been prescribed, it was decided to use the neo-salvarsan. An initial dose of 0.30. was injected and within 24 hours, more or less, the temperature had dropped to normal and all the distressing symptoms had subsided. Successive and increasing doses of neo-salvarsan were given every 7 days until 6 treatments had been completed, at the termination of which the patients felt very well indeed. However, I must bring to your attention the fact that, notwithstanding this treatment, subsequent examinations made of the sputum always revealed the presence of the *Spirochaeta bronchialis*, indicating, therefore, that, while the use of neo-salvarsan made the most distressing symptoms disappear, the presence of the spirochaetes prevailed, — and it was so even 2 months after the last injection had been given.

Dr. H. C. Clark. — I have no personal experience with such cases of bronchial affections, but it might be in order for me to refer to a few cases of *Spirochaetosis bronchialis* reported by Drs. Bates and Briscoe of the Canal Zone.

Following the epidemic of influenza in 1919 and 1920, we had some cases who drifted into a chronic course of respiratory illness. Usually tuberculosis or *bronchiectasis* is expected in such people, but there were 5 or 6 individuals who were outside these groups, so far as any of our laboratory or X-ray examinations could determine. We began, then, to look for what we considered the more remote

possibilities, such as mycotic disease and *spirochaetosis*. The latter was established by dark-field and stained-smear examinations. The people were either cured, or so greatly improved by the administration of potassium iodide, that they were discharged. I have not yet seen such a case in Honduras. I have never seen a case of mycotic bronchitis that was not associated with tuberculosis. This statement is not offered as any reflection on a possible primary condition of this nature, however.

I am sure that we overlook many lesions of a mycotic nature. I, for one, can never be sure whether a fungus that I find is important or non-important when it comes from the body covering, the respiratory tract, or the alimentary tract. A few cases of *mycosis* come to mind, in which I am convinced of their pathogenic importance, but I cannot offer any identification data regarding their type. Our commonest disease of this nature is chronic *otomycosis externa*. These cases reveal a fungus or fungi which grow out as pink, lemon or black colonies.

We have had one case of bilateral inguinal *lymphadenitis* due to a black fungus. This case had a gland excised for diagnosis and culture work but no further surgical work was needed, since the administration of potassium iodide cured him. There was one case of femoral *lymphadenitis* due to an acid-fast streptothrix which, for all I know, may represent one of the fungus group.

A young girl of about 16 years came to us for laboratory work. She suffered from a disease of the soles of the feet, of several years' duration. The extremities were greatly thickened, and there was constant shedding of epidermis. We could find nothing except a fungus that might be the cause of the trouble, and I have since learned that this diagnosis was confirmed in Europe.

Since arriving in Honduras, I have seen only one case that struck me as being a serious mycotic disease. This was in a male native and involved the mucosa of the lips, cheeks, tongue, naso-pharynx and larynx. The man could speak only in a whisper. It looked like a severe case of thrush, but there was abundant bleeding from the mucosa and the smears were quite unlike the thrush fungus. It was arranged like the ray-fungus but without clubbed ends. The man recovered after several months, but was never able to speak above a whisper.

We need Dr. Castellani's instruction, for I am sure it is very necessary in the Tropics and that many interesting cases are overlooked, insufficiently recorded, and not treated in a specific manner.

Sir Thomas Oliver. — I am very much obliged to Dr. Deeks for the opportunity he has given me of expressing my appreciation of the paper which Dr. Castellani has read, and of the important

contribution he has made to the subject of parasitic diseases of the lungs. As a physician, I am naturally interested in anything that concerns the relationship of pulmonary tuberculosis and other diseases of the lung. What struck me at first in Dr. Castellani's remarks, was the reference to haemorrhages which occurred in *Broncho-spirochaetosis.*

I am going to ask Dr. Castellani whether he would be kind enough to explain what he regards as the cause of the pulmonary haemorrhage. I rather gathered that haemorrhages occurred at the particular time when there were many spirochaetes in the blood, and therefore that the *haemoptysis* might be due to a spirochaetal *thrombosis.* On the other hand, there are the haemorrhages known to occur in bronchial *Moniliasis.* Bronchial *Moniliasis* seems to be an affection probably carried into the lungs by the air, and therefore a local infection. I was particularly interested in the results which he obtained by inoculation, first of the sputum with no result, and then of injection of culture followed by results.

I raise a question as to whether the bronchitis is primary or secondary, for when an intravenous injection of very fine particles of aluminium ore is made into animals the aluminium particles are taken up by the leucocytes of the blood, so that when the lungs of the animals are examined the leucocytes or phagocytes are seen passing out from the pulmonary capillaries into the alveoli of the lung, and thence into the bronchi. In the smaller bronchi numerous phagocytes can be observed, containing many particles of the bauxite accompanied by a considerable quantity of mucous secretion. The condition is an illustration of a secondary bronchitis induced by the passing out of the ladened leucocytes into the pulmonary alveoli, and subsequently into the bronchioles.

I would like to mention one other point. I rather gathered that haemorrhage, in these mycotic infections, comes on rather late in the disease. Dr. Castellani, in contrasting this with the *haemoptysis* occurring in tuberculosis, remarked that the haemoptysis of tuberculosis comes on in the late stages of that disease, and that therefore little can be done for the patients. We must not forget, however, that haemorrhage may occur in the early stage of pulmonary tuberculosis and be due, not to nodules which are disintegrating, but to the probability of a limited environmental acute congestion.

Dr. Aldo Castellani (*Closing the Discussion of His Own Paper*). — I was very much interested in the remarks made by Dr. Johns. I quite agree with him that we are giving too much importance to the X-ray examination in the diagnosis of tuberculosis. There is no doubt that, in certain cases, *Broncho-spirochaetosis* and certain

forms of *Broncho-mycosis* give the same picture. I may mention some interesting observations made by Fahra in Egypt: — Practically all his cases of *Broncho-spirochaetosis* and *Broncho-mycosis* had been examined by an X-ray specialist and diagnosed as pulmonary tuberculosis.

Dr. Iturbe's remarks on *Paragonimus Ringeri* were, as usual, extremely interesting.

Colonel Ashford's case of pulmonary abscess of monilial origin, cured by a monilial vaccine, is of great practical importance.

I was also very much interested in the remarks made by Dr. Facio and by Dr. Clark. Dr. Facio treated his patients with salvarsan and neo-salvarsan, and noted that the acute symptoms disappeared but some spirochaetes remained in the sputum. In these cases it is advantageous to give also tartar emetic. It may be given intravenously or by the mouth. I agree with Dr. Clark that in certain cases potassium iodide is more effective than tartar emetic or arsenic. Fahra had the same experience in Egypt, and found that most of his cases did well on lipiodol, which is an iodine preparation dissolved in oil.

Dr. Clark has given us some exceedingly interesting remarks on certain mycoses of the glands of the inguinal region. I had somewhat similar cases in Ceylon, and fairly recently had a case in London which must be of practically the same nature. In my cases I grew fungi of the genus *Sporotrichum* and the genus *Chladosporium*.

Sir Thomas Oliver has asked me whether the haemorrhages in *Broncho-mycosis*, and principally in *Broncho-monoliasis*, take place at an early or very late stage of the disease. My experience is that they may take place in any stage, but more frequently occur in the late stages.

I think it most important that we should distinguish between primary and secondary *Broncho-moniliasis*. In primary *Broncho-moniliasis* the isolated *Monilia* will be virulent to the rabbit when injected intravenously, and when the injection is intrapulmonary will produce a very characteristic nodular condition of the lungs within 2 to 3 weeks.

THE INJECTION OF SERUM OR PLASMA FROM CONVALESCENT CASES OF MEASLES, TO PREVENT THE DEVELOPMENT OF THE DISEASE IN CHILDREN

William H. Park, M.D.

Evidence has been accumulating for the past 30 years, and especially within the past 5 years, that the serum withdrawn 6 to 10 days, and later, after convalescence from measles contains potent antibodies. This serum has been utilized successfully to immunize persons not exposed for over 6 days, and to lessen the severity of the disease when it developed, if given up to the time of the development of the rash.

Recently Degwitz utilized it in hundreds of cases, and suggested the following dosage:

2.5 cc. in those exposed 4 days or less
5 cc. " " " 6 " " "
7 cc. " " " 7 " " "

With those exposed more than 7 days he was unsuccessful.

During the past three years we have used the serum successfully in our contagious disease hospitals to prevent infection in children who had been exposed to cases of measles developing in the wards. The results of its use have been so successful that it seemed to me it should have a wider use and should be made available for all children's institutions and for all children under three, when the development of measles might be followed by a complicating pneumonia.

Before we could undertake to use the convalescent serum for this purpose, it was necessary to obtain a large supply. This we were able to do through the coöperation of Dr. Carley, the physician to Berea College. Sixty adults who had recently recovered from an attack of measles, and who

had given a negative Wassermann test, were bled and in order to utilize all the antibody we used the plasma instead of the serum. The plasma was preserved from clotting, by Sodium Citrate, and from bacterial contamination by chinosal. The plasma was separated from the blood-cells by centrifuging it.

Repeated bleedings are being taken from the group of college students from time to time, and the mixed plasma is being partly used and partly stored, so that in time we shall be enabled to determine the duration of antibodies in the recovered patient and in the stored antibody plasma. Before being used, the plasma was tested for sterility and placed in 6 cc. vials. These were distributed to the different parts of the city. Physicians could obtain it on request, but only after filling out a blank giving the desired information. Dr. R. G. Freeman, Jr., an inspector, was detailed to care for the children in institutions and to administer plasma to the exposed children with the least possible delay. He was also responsible for obtaining and tabulating all facts as to the exposure and the later history of the cases. At first we gave only 3 cc., but soon realized that 5 to 6 cc. were required. This was for children who had been exposed for not over 4 days — 10 cc. were required for children over 3 years of age, or who had been exposed more than 4 days.

We have injected over 1,500 children; but we had *records*, at the time of my writing, of only 979 children.

THE RESULTS OBTAINED IN NEW YORK CITY

Over 1,500 children received preventive injections between December 1st and June 1st. From 979 we have fairly accurate data as to the date of exposure, the degree of exposure, the amount of plasma injected, and the success attained.

Of these 979 children, 753 were exposed in institutions and 226 in private families. In 404 of the institutional children, and in all of the children in families, the exposure was direct. In 349 it was indirect, in that actual personal contact with a measles case was not proved.

INSTITUTIONAL CHILDREN

Amount Plasma Injected	Number Children	Modified Measles	Unmodified Measles	Complete Success	Incomplete Success
3 cc.	219	20%	8%	72%	92%
4 and 5 cc.	190	8%	2%	90%	98%
6 to 10 cc.	243	6%	2%	92%	98%
Total in Institutions	753	11%	5%	84%	95%
Total in Families	226	42%	5%	52%	95%

No bad effect followed the injections in any case. Only one of the children died, and this one had an empyema before contracting modified measles and was but 2 years of age.

CONCLUSIONS

The injection of 6 cc. of convalescent serum into a child under 3 years of age, and 10 cc. for a child over that age, who has been exposed for less than 5 days to measles, is sufficient, as a rule, to prevent infection. If it does not, it almost certainly so modifies the attack that it is very mild and not liable to lead to complications.

The prompt use of the serum will prevent outbreaks of measles from developing in institutions, and so prevent complicating pneumonias.

It would be of extreme value to have a supply on hand to prevent outbreaks of measles among troops, such as occurred so disastrously in the late war.

The serum gives immunity for only one month. The modified cases have a lasting immunity.

The serum contains the greatest accumulation of anti-bodies shortly after the convalescence of the patient. At the end of 3 months the anti-bodies are much less in amount.

PATHOLOGY IN THE TROPICS

FRANK B. MALLORY, M.D.

(Read by Title)

Most of the work done so far in medicine in the tropics has been, necessarily, first the study of the symptoms, and then the treatment, of the diseases peculiar to that part of the world, followed later by the search for the causes of them. Great progress has been made especially in determining the etiology of many of the infectious processes such as malaria, filariasis, yaws, etc. As a result treatment has been put on a much more intelligent basis and absolute prevention of many of the infections rendered possible. In all the investigations into the causes of tropical diseases, and into the cell changes taking place in the lesions produced, pathology has played a prominent part. It is of interest, therefore, to inquire what are the possibilities still open in the tropics to this fundamental branch of the scientific side of medicine.

To put pathology on a firm basis and to enable it to accomplish the things of which it is capable, arrangements should be made so that all pathological material can be examined in a routine manner in exactly the same way that every patient is gone over thoroughly by the clinician. This means either establishing a pathological laboratory in connection with every large hospital, or making arrangements with such a laboratory elsewhere, so that tissues of all sorts from hospitals large and small can be sent to it for examination, study and diagnosis. Only in this way, by the routine examination of all material, will it be possible to discover unsuspected and new lesions and to clear up cases which have proved puzzling. In the United States no hospital can be ranked in class A which does not have at its command the services of a competent pathologist.

The performance of an autopsy in every instance possible has certain important advantages. In the first place it teaches the clinicians by showing them exactly what they were trying to cure and stimulates them to thoroughness and

accuracy in their work because the post mortem findings serve as a valuable check on their clinical diagnoses. The result is better service for the patients. A recent case, which had gone through a large hospital and had come up for discussion before the students, was diagnosed clinically as chronic myocarditis. The pathological finding was acute miliary tuberculosis with no lesion of the heart. Unless clinicians have such cases as this brought to their attention they can go on indefinitely making incorrect diagnoses.

Routine examination of autopsy material has shown, for example, that death may be caused by carbon tetrachloride now so extensively used in the treatment of hook-worm disease. This substance, like chloroform to which it is chemically closely related, sometimes causes extensive necrosis of the cells of the liver and to a less extent of those of some of the other organs. The obvious deduction is to build up the physical condition of run down patients before subjecting them to the treatment or to diminish the size of the dose.

The study of all the organs from more cases of blackwater fever might throw some light on the cause of the hemoglobinuria. It is difficult to see how the common malarial parasites which ordinarily cause the formation of dark granules of an insoluble pigment (hematin) can under certain conditions produce hemolysis and hemoglobinemia with the resulting hemoglobinuria. Two cases studied have shown very little granular pigment in the spleen and other organs. The condition has suggested to some observers the action of some other parasite which causes hemolysis. Only further study and observation can finally clear up the problem to the satisfaction of the men holding different views.

Secondly, the routine examination of all surgical specimens almost always renders possible an exact diagnosis of the pathological condition present, so that the proper treatment can be adopted, and sometimes throws light on a case where the lesion present was not suspected, as, for example, the finding of the organisms of granuloma inguinale in an obstinate balanitis. In another instance a lesion of the back of the hand diagnosed clinically as epidermoid carcinoma proved on microscopic examination to be due to chronic yaws and yielded to simple treatment, the necessity of a serious operation being thereby avoided.

The third reason for routine pathological examination of all diseased tissues removed surgically or obtained post mortem is that material is thus rendered available for careful study of all the cell changes taking place in the different lesions and this enables one to obtain a better idea of the processes going on. A certain number of the observations made and results acquired in this way are worth putting on record. Some are of purely pathological interest, others are of benefit to the clinician. Single cases are sometimes of great interest and value. In other instances it requires years to accumulate enough material to be able to make out of it a valuable contribution to our present knowledge. For the solution of obscure processes such as ainhum, for instance, a series of cases of this puzzling lesion at different time periods must be secured before it will be possible by the study of all of them to trace and understand the changes which take place.

Prevention of disease will eventually form the highest type of treatment but before that can be employed disease processes must be understood and the causes of them fully ascertained. This is the province of pathology in the future as in the past. Much still remains to be done. The more obvious problems have been solved or are in the process of solution. The more difficult and obscure ones will require concentrated, long-continued investigation. This is the field in which high class, persistent, routine work and study will help greatly, and will unquestionably clear up some at least of the pathological problems which still trouble the medical world.

THE DEVELOPMENT OF PATHOGENICITY AND PARASITISM IN SAPROPHYTIC MICROÖRGANISMS THROUGH CHANGED ENVIRONMENT

Richard P. Strong, M.D.

(Read by Title)

Many of the districts in which the United Fruit Company has developed its tropical stations, before their transmission into healthy localities by sanitary measures, constituted natural incubators for disease. Heat, moisture, fertility of soil, and abundant vegetation all favored the multiplication of many microörganisms which have been termed "free living" or "saprophytic," and the conditions of life which formerly prevailed in these districts, and which still prevail in some of the surrounding areas, have furnished abundant opportunities for the transmission of these microörganisms to higher forms of animal life, and for the gradual development of pathogenicity and parasitism by these microörganisms for their new hosts.

It therefore seems appropriate on this occasion, — which in a way is a demonstration of the success which the Medical Department of this Company has had in dealing with the disease problems in its tropical stations, — to review the progress of our knowledge of the broader outlines of biological development in respect to some of those microörganisms which at least during one stage of their existence may be referred to as free-living or saprophytic, or symbiotic, and of their potentiality in a different environment to assume a parasitic existence and produce disease.

I have recently had an opportunity in Panama and in the laboratories of the United Fruit Company in Spanish Honduras, to carry on some investigations with reference to the development of parasitism by the nematode connected with that important disease known as the red ring of the coconut, and therefore I shall first ask your consideration of the ques-

tion of the development of parasitism among some examples of this group of organisms.

We find many striking examples among the *nematodes* and *helminths* in general of the efforts on the part of Nature to perpetuate her species through the establishment of parasitism in which alternating and differently formed generations and cycles of development in intermediate hosts have resulted. From many of these examples it seems natural to conclude that the development of parasitism as well as of a change of host have been gradual transitions. Moniez[1] believes that all entozoa may be traced from saprophytes, only a few of which have been able to settle directly in the intestine and there continue their development; these are forms such as *Trichocephalus*, *Ascaris*, and *Oxyuris* which still lack an intermediate host. However, in many other cases the embryos consisted of such saprophytes as were in other respects suitable to become parasites, but were incapable of resisting the mechanical and chemical influences of the intestinal contents. They were, therefore, obliged if they were to continue to exist, to leave the intestine and they accomplished this by penetrating the intestinal walls and burrowing into the tissues of their animal carriers. Later, by the ingestion for food by beasts of prey, of some of these carriers, they passively reached the intestine of their new host and there, having become more capable of resistance, attained their maturity. By means of these incidental coincidences of various favorable circumstances these processes of parasitism, according to Moniez, have been gradually established. In the nematodes there are numerous examples of free-living members from which it seems probable that the parasitic species may be descended. Such examples are witnessed in *Leptodera*, *Rhabdonema*, and *Strongyloides*. These mostly, if not exclusively, spend their lives in places where decomposing organic substances are present. Some species attain maturity only in such localities. Should the favorable conditions for feeding be changed, the animals may seek out other localities. It is understandable that such forms are very likely to adopt a parasitic manner of life which at first is facultative, as in *Leptodera* and *Anguillula*, but may be regarded as the

[1] MONIEZ; *Trait. de Parasit. Anim. et Veg.*, Paris, 1896, 8 vo.

transition to true parasitism. In many forms the young stages live free for some time, as in *Strongyloides;* in others, as in the case of *Rhabdonema*, parasitic and free-living generations alternate. A most striking example of a free-living (*Rhabditis*) generation passed in the soil, and a parasitic strongyloid, one which occurs in the intestine of man, is seen in *Strongyloides intestinalis*[1]. Infection of man occurs through penetration of the filariform larvae through the skin, in the manner of hookworm larvae, the embryo migrating through the lungs before becoming parasitic in the intestinal wall.

The genus *Aphelenchus* is of particular interest in that at least six of the species are recognized as pathogenic for plants — some causing serious agricultural pests. The genus comprises between thirty and forty species the majority of which are free-living forms occurring in association with the roots of plants, in moist humus, or in water. The two species known to be of most agricultural importance are *Aphelenchus fragariae*, Ritzema-Bos, 1891, and *Aphelenchus cocophilus*, Cobb, 1919. The former is endoparasitic in the stems of strawberry plants, where it causes hypertrophy and the production of "cauliflower" disease, or it may be ectoparasitic in the buds of the strawberry causing the "red plant disease." The latter (*Aphelenchus cocophilus*) occurs endoparasitically in the stem, leaf, and roots of the coconut palm, particularly in the West Indies, and portions of Central America. "Red ring disease" of the coconut palm, also previously known as "Trinidad root disease," has been studied recently particularly by Nowell[2], Cobb[3], and Zetek[4]. The diseased trees show a progressive yellowing and browning of the leaves commencing at the leaf-tip; the nuts are shed slightly in advance of the discoloration of the leaves and in a green condition and this may be the first external evidence of the affection. On section the stem shows a well-marked complete ring of reddish-brown tissue usually from one to one and a half inches in width and lying about from one to two inches from the periphery of the stalk. The diseased tissue may

[1] STRONG; *Johns Hopkins Hosp. Reports*, 1902, X, No. III.

[2] NOWELL; *West Indian Bull.*, 1919, XVII, 189.

[3] COBB; *ibid*, p. 203.

[4] ZETEK; *U. S. Dept. of Agricul. Bull.* No. 1232, 1924

extend up the stem for several feet and then become broken into longitudinal streaks and irregular small patches. Leaf stalks may also show these same pathological changes. The roots become affected in the cortex, first undergoing yellowish or pinkish discoloration and softening, later becoming brownish red and sometimes dry and flaky. Infection experiments have been conducted by Nowell, Cobb and Zetek in which portions of diseased tissue containing the nematodes have been inserted into healthy palms with the result that the typical diseased conditions have been set up. The adult male and female nematodes occur abundantly in the roots in the areas where the tissues are softened and yellowish to brownish-red in color. The eggs are deposited in the tissues of the plant where they hatch out and the larvae invade fresh tissues. The larvae are found not only in the roots but also in enormous numbers throughout the diseased tissues. While the habits of these species outside the host plant have not been thoroughly studied, it seems reasonable to suppose that on the falling of diseased leaves or trunks the nematodes would ultimately find their way to the surface of the soil and the subjacent layers, and that infection of the young plants might take place by the migration of the nematodes from the soil to the new plant. It has been shown that the nematodes will live in the soil about an infected palm. Very recently Zetek has made observations which have led him to suggest that the termite, *Coptotermes niger* (Snyder) may be a mechanical carrier of this nematode from the old host to the new plant, he having demonstrated nematodes clinging to the bodies of the termites which were living in a coconut palm infected with "red ring."

The writer has, as intimated, been able to study the disease in Panama and particularly in Spanish Honduras. While it would appear that the nematodes in question are certainly concerned in the production of the disease, the lesions produced in the palm consisting of the softening of the tissues, their liquefaction and subsequent necrosis, are not such as are usually attributed to nematodes. Both with the idea of acquiring information regarding the presence of some additional pathogenic agent in the disease, and also of ascertaining any pathogenic action of the nematodes, not only for the plant, but for animals, inoculations of suspen-

sions of the nematodes in saline solution into mice, guinea pigs and rabbits were undertaken. The guinea pigs were inoculated intraperitoneally, subcutaneously, or intraintestinally. The mice were inoculated subcutaneously and the rabbits intravenously or subcutaneously. When the injections were made intraperitoneally into guinea pigs the death of the animals often occurred, in which there was a general peritonitis associated with a short bacillus, but no nematodes were found in the peritoneal fluid, the blood or other organs of the animal. In fact, after intraperitoneal inoculation the nematodes were never found alive in drops of fluid withdrawn by a capillary pipette from the abdominal cavity longer than two and one-half hours after the time of the inoculation. In the guinea pigs which were inoculated by injecting the fluid containing the nematodes through the peritoneal cavity and walls of the intestine directly into the lumen, the nematodes were not subsequently found in the faeces of the animal. Some of the rabbits which were inoculated intravenously also died, in which bacilli were isolated from the blood and liver, but no nematodes were found in these situations. In none of the experiments was any pathogenicity of the nematodes for these laboratory animals demonstrated. Cultures were made from the lesions of "red ring" after burning the surface of the palm, and in practically all instances species of fungi or bacilli were cultivated. More confirmatory observations must be made before we can conclude that the lesions of "red ring" are produced solely by *Aphelenchus*. Perhaps *Aphelenchus* may also mechanically carry bacteria with it into the tissues of the plant, or offer a more favorable portal of entry for other microörganisms. Obviously, termites do not serve as the infective agent in many cases because in many coconut palms infected with "red ring" no infestation with termites is present. Therefore, in the case of *Aphelenchus* so far as our knowledge goes, parasitism has apparently developed for plant rather than for animal life.

There has been some difference of opinion as to whether or not some of those *spirochaetes* which have been supposed to be purely saprophytic and to lead a free existence, might, under other conditions, acquire pathogenic properties. It has been suggested that by mutation and adaptation they may in some instances be able to become transformed from

harmless saprophytes into highly pathogenic parasites. Neumann[1] believes that non-parasitic, saprophytic spirochaetes can rather quickly change in character and acquire pathogenic properties. He calls attention to the fact that two of his experimental rabbits acquired genital spirochaetosis through contamination by manure which contained the microörganisms. Other observers have objected to these conclusions and believe that in Neumann's experiments in rabbits, the possibility of infection of the wounds with spirochaetes from the intestine was not excluded. Moreover, Warthin, Buffington and Wanstrom[2] have recently emphasized the fact that infection with a form of spontaneous venereal spirochaetosis in rabbits may occur and spread by both contact with other infected rabbits or by coition. Worms[3] has also claimed to have induced typical genital spirochaetosis in rabbits by inoculating them with *Spirochaeta dentium* of the normal human mouth, but it has also been objected that no proof is given that the spirochaetes which persisted in the lesions were actually pathogenic to the animals, and that they might merely have survived as saprophytes.

In this connection some studies have recently been carried out with the presumably saprophytic species of spirochaetes found in the human intestine. Werner, in 1909, described two types of spirochaetes found in his own stool after typhoid fever. One of these he named *Spirochaeta eurygyrata* which was loosely coiled, very active and flexible, with rarely more than two spirilla, mostly as "S" forms. The other type, called *Spirochaeta stenogyrata*, was tightly coiled, not so active and less flexible. It is well recognized that in apparently healthy persons spirochaetes may be sometimes found in small numbers in the faeces, and that in other individuals suffering with some form of colitis, enormous numbers of spirochaetes are sometimes encountered. In the latter instance, *Spirochaeta eurygyrata* has often been regarded as the excitant factor. Le Dantec, Luger and others have believed that the intestinal spirochaetes may give rise to a form of dysentery. However, the investigations of Muhlens, Macfie, Pons and others suggest that at times at least this

[1] NEUMANN; *Central. f. Bakt.*, 1923, XC, Heft 2, 100.

[2] WARTHIN, BUFFINGTON and WANSTROM; *Jour. Infect. Dis.*, 1923 XXXII, 315.

[3] WORMS; *Klin. Woch.*, 1923, 836.

spirochaete may exist in the intestine as a harmless saprophyte. Delamare[1] has raised the question of the intensity of infection with spirochaetes in the human intestine which indicates the border-line between health and disease. From his investigations he regards from six to ten spirochaetes per microscopic field as the standard to adopt. He believes that the spirochaetes multiply rapidly when the intestine is in a condition favorable to their growth, such for example as exists in cholera or in amoebic dysentery. Without attributing any pathogenic properties to the spirochaetes in this locality, he believes their presence in large numbers is nevertheless an indication that the intestine and especially the colon is in an abnormal condition. Parr[2] has found that spirochaetes can be demonstrated in about one-third of the healthy persons about Chicago, though the intensity of the infection in healthy persons is slight. The spirochaetes were localized in the caecum and ascending colon and in many cases did not appear in the faeces.

Attempts successfully to infect animals with *Spirochaeta eurygyrata* and similar intestinal spirochaetes have not been conclusive.

Blanchard[3] is reported to have introduced the exudate from the false membrane of a case of Vincent's angina into the digestive tube of a dog and produced a dysenteriform state in the animal in which both spirochaetes and fusiform bacilli were recovered from the stools. However, Tanon who studied the effects of subcutaneous, intravenous and intraperitoneal injections of spirochaetal intestinal material into guinea pigs, rabbits, and monkeys, only obtained negative results.

Teissier and Richet[4] also fed rabbits and guinea pigs faecal suspensions rich in spirochaetes and obtained only negative results. When the material was injected subcutaneously, abscesses were formed, but they contained no spirochaetes. When intraperitoneal injections were made into guinea pigs, the peritoneal cavity was found to be subsequently rich in

[1] DELAMARE; *Bull. et. Mem. Soc. Med. Hopit. de Paris*, 1924, XLVIII, 725.

[2] PARR; *Jour. Infect. Dis.*, 1923, XXXIII, 369.

[3] BLANCHARD; cited by Hassenforder. Thesis. Lyons, 1914.

[4] TEISSIER and RICHET; *Bull. et Mem. Soc. Med. Hopit. de Paris*, 1911, XXXI, 775.

spirochaetes, but when some of the fluid was injected into a second series of guinea pigs, no spirochaetes were obtained. Hassenforder[1] reported positive results only when the faecal suspensions containing spirochaetes were associated with virulent amoebae and injected intrarectally into cats.

Hogue[2] fed three cats 6 cc. of a culture of *Spirochaeta eurygyrata*, but no spirochaetes were subsequently found in the stools.

Parr[3] injected faeces containing spirochaetes intraperitoneally into six guinea pigs and in no case was an abdominal exudate found containing spirochaetes. Intratesticular injections in rabbits were also negative. The exact nature of the material injected and the approximate number of spirochaetes in it is not stated. Apparently the fusiform bacillus was not present.

Broughton-Alcock,[4] however, attaches a definite etiological significance to *Spirochaeta eurygyrata* in certain chronic and intermittent cases of dysentery, and he found that the organism occurs in great numbers in the mucus passed in the acute and subacute stage of such cases when no other microörganism is present to account for the pathological condition. His experience has led him to believe that *Spirochaeta eurygyrata* can produce in human beings a catarrhal condition of the intestine with the passage of mucus containing shed degenerated epithelial cells, occasionally red blood cells, and, rarely, typical dysenteric symptoms. He adds that there is always the argument that a primary agent has produced a vulnerable surface over which the organism acts symbiotically. The idea of the spirochaete having acquired pathogenic properties or an increased virulence in this condition, is not suggested, but he believes that the spirochaete of somewhat similar but not identical form found in the normal faeces is *Spirochaeta stenogyrata* which is non-pathogenic, *Spirochaeta eurygyrata* being found only in the mucus and not in the faeces. Attempts to infect mice with *Spirochaeta eurygyrata* were unsuccessful. Davis and

[1] HASSENFORDER; Thesis. Lyons, 1914.

[2] HOGUE; *Jour. Exper. Med.*, 1922, XXXVI, 617.

[3] PARR; *Jour. Infect. Dis.*, 1923, XXXIII, 379.

[4] BROUGHTON-ALCOCK; *Proc. Roy. Soc. Med.*, 1923, XVI, Pt. 3, p. 46.

Pilot[1] believe that some cases of gangrenous appendicitis appear to arise from the fusiform bacilli and spirochaetes of the intestine which have acquired a new virulence.

The relationship to bronchial spirochaetosis of *Spirochaeta bronchialis* (morphologically similar to *Spirochaeta vincenti*, *Spirochaeta schaudinni*, and *Spirochaeta refringens*) raises the question of whether there is an acquired pathogenesis for this species in this condition. The recent investigations of Pons[2] further substantiate the view that the spirochaetes in the sputum in bronchial spirochaetosis are really similar to those described as occurring in the human mouth by many observers and that possibly they may have found in this pathological condition in the bronchi a suitable medium for further development. Perhaps such a favorable medium also occurs in tuberculosis and in certain other pathological conditions of the lung. Trocello has expressed the view that the oral spirochaetes can extend directly to the bronchi. Pons studied nine cases of bronchial spirochaetosis and came to the conclusion that it was impossible to confirm deMello's[3] observations that the bronchial spirochaetes are distinct from those of the mouth. He was not able to differentiate *Spirochaeta buccalis* from *Spirochaeta bronchialis*. He was also not able to confirm such statements as those which affirm that the oral forms are less motile and retain their motility longer than the bronchial forms, and do not produce the coccoid bodies to the same extent. He, however, did observe a rapid loss of motility in the bronchial forms. Attempts to reproduce the disease, bronchial spirochaetosis, by intratracheal inoculation of normal rabbits, failed. He, however, does not believe that the spirochaetes encountered in pathological conditions of the lung are purely saprophytic but rather that they afford evidence of an abnormal condition due to varying causes, and that they are able to give to these conditions characteristics such as chronicity and ulceration which one is accustomed to associate with the occurrence of spirochaetes in a lesion.

Obviously still further investigation is desirable upon the

[1] DAVIS and PILOT; Collected Studies from the Dept. of Pathology and Bacteriology, Univ. of Illinois, Chicago, 1922–23, p. 27.

[2] PONS; *Bull. Soc. Path. Exot.*, 1924, XVII, 170.

[3] DEMELLO; *Bol. Geral. Med. et Farmacia*, Bastora, 1924, Feb., 9th series, p. 46.

question of the pathogenicity under some circumstances and under the influence of some possibly symbiotic microörganism or bacteriophage, of *Spirochaeta bronchialis* and the morphologically similar forms.

In the mouth and from the genital organs of some individuals spirochaetes have been observed living apparently as harmless saprophytes which are morphologically indistinguishable from some of the well recognized pathogenic species. These organisms have been found in association with fusiform gram-negative bacilli not only in these situations but particularly in the lesions about carious teeth and in gangrenous putrid infections about the mouth. Broughton-Alcock[1] has found spirochaetes with other bacteria in a catarrhal exudate from the antrum, and Tunnicliff has observed them in a frontal sinus. Davis and Pilot[2] have recently emphasized the importance of the occurrence of spirochaetes and fusiform bacilli not only in Vincent's angina but in ulceromembranous stomatitis, noma, putrid otitis media, putrid bronchitis, and gangrenous pneumonia. They believe that such conditions are usually caused by these organisms which presumably come from the mouth or tonsils or both. They also conclude that the several gangrenous processes that occur at times about the male and female genitals presumably result from invasion by these organisms that occur normally there. They inoculated material containing fusiform bacilli and spirochaetes and pyogenic cocci from teeth, tonsils, smegma, and putrid sputum, both intrapleurally and subcutaneously into rabbits, and obtained putrid and gangrenous lesions containing these organisms. The cocci, especially streptococci, were found to be the most aggressive organisms and sometimes alone invaded the adjacent cavities and the blood stream. The fusiform and spirochaetal organisms tended to remain more local, causing necrosis and gangrene in the already invaded tissues. Predisposing factors are considered usually as of first importance in determining the development of the microörganisms, and they believe that at times they may, like bacteria, develop a degree

[1] BROUGHTON-ALCOCK; *Trans. Roy. Soc. Trop. Med. & Hyg.*, 1923, 337.

[2] DAVIS and PILOT; Collected Studies from the Dept. of Pathology and Bacteriology, Univ. of Illinois, Chicago, 1922–23, p. 27.

of virulence sufficient to enable them to gain a foothold in the normal tissue.

The free-living spirochaetes of water have generally been considered as saprophytic organisms. They have been found in fresh and in marine water, often more particularly when the water is stagnant and when through the decomposition of protein in the presence of ammonia, nitrites and nitrates, hydrogen sulphide gas is freely generated. They are also often found on the surface of filters, about the apertures of water taps, and on the under-surface of metal closure caps of certain bottled drinking waters in northern Brazil. A number of these spirochaetes correspond morphologically with the parasitic species such as *Treponema pallidum* of syphilis, *Leptospira icterohaemorrhagiae* of Weil's disease, *Spirillum obermeieri* of relapsing fever, and *Spirochaeta hebdomadis* of seven-day fever. We have referred to the fact that in the mouth and in the genitals of some healthy human beings there occur spirochaetes which are morphologically indistinguishable from certain of the well known pathogenic species such, for example, as some of those just enumerated, but several of these spirochaetes from the mouth and genitals are also morphologically indistinguishable from some of the spirochaetes found recently in water. Evidently, therefore, morphological resemblances alone are entirely insufficient for us longer to attempt to differentiate spirochaetes generally into different species, nor are they obviously sufficient for us to establish the identity of a number of these water spirochaetes with some of the species known to cause disease. Animal inoculations in some instances, however, have furnished additional evidence in this respect.

Spirochaeta schaudinni, morphologically identical with *Spirochaeta vincenti* and *Spirochaeta refringens*, has been encountered by many observers in open ulcers of the skin.

Very often the spirochaetes in such lesions have been found associated with fusiform bacillary forms. These organisms in certain localities and lesions are practically always associated. By some observers they are regarded as distinct organisms, perhaps living symbiotically, while by others the fusiform bacilli and spirochaetes are believed to be merely different forms in the life-cycle of one organism.

Ruth Tunnicliff[1] holds the latter view. She admits, however, that there are several different strains of fusiform bacilli.

In portions of northern and central Brazil, chronic ulcerative processes of the skin are exceedingly common and in one form of tropical ulcer, *Spirochaeta vincenti* and fusiform bacilli are invariably present and apparently constitute the most important etiological factor in this particular form of ulcer. The spirochaetes and fusiform bacilli are found in abundance not only on the surface of the lesions, but usually extending for at least several millimeters into the tissue surrounding the ulcer. Numerous cocci and other bacilli are also usually encountered in the exudate upon the surface of the ulcers. Small pieces of tissue were removed from a number of these ulcers and after they had been thoroughly rinsed in sterile normal saline solution were ground up in a mortar, resuspended in other saline solution, and the suspension injected subcutaneously into monkeys and also intratesticularly, after injury, into rabbits. Suppurative and ulcerative lesions were produced in these animals thereby, in which both spirochaetes and fusiform bacilli as well as cocci were found present.

It seems probable that *Spirochaeta vincenti* cannot usually establish itself in healthy skin or even in many aseptic wounds, but if the integument is bruised or otherwise injured and the circulation interfered with and the vitality of the tissues otherwise impaired, it may often assume pathogenic properties and a phagedenic ulceration result. The recent observations of Van Nitsen[2] are also in accord with this view.

In view of the fact that there are in some waters spirochaetes which are morphologically indistinct, or very similar to *Spirochaeta vincenti*, experiments were undertaken to see if these spirochaetes were also pathogenic for animals. In Manaos various samples of stagnant water and scrapings from the surface of filters, and apertures of water taps, and under-surface of caps of mineral water bottles, were suspended in saline solution, were centrifuged, and the sediments which contained spirochaetes resuspended in saline

[1] TUNNICLIFF; *Jour. Infect. Dis.*, 1923, XXXIII, 147.

[2] VAN NITSEN; *Annales Soc. Belge de Med. Trop.* 1924, III, 317.

solution and injected subcutaneously and intraperitoneally into mice and guinea pigs and subcutaneously into monkeys.

Only negative results were obtained. The animals remained healthy, and we were entirely unable to produce any lesions such as had been done with the material obtained from the tropical ulcers. Our experiments with the spirochaetes from tropical waters, however, are far from being complete and are not conclusive, since the spirochaetes employed in our inoculations were never obtained and injected in large numbers. On my return to this country I found that Noguchi[1] had studied some of the spirochaetes which he had isolated from more or less stagnant ponds, swamps, and ditches in the northern United States, and had previously reported on this study. He obtained growth of the water leptospiras in impure culture on his regular leptospira media, though with considerable difficulty. Inoculations of the leptospira water samples into guinea pigs, white rats, and mice, were repeatedly made, but no infection could be induced in the animals. His injections of cultures likewise proved to be harmless. The kidneys and liver of the inoculated rats were removed after three weeks and suspensions of these organs injected into guinea pigs with the hope that passage through rats might have enhanced the virulence of the organisms but no positive results were obtained. He concluded that the water leptospiras which he studied appeared to be non-pathogenic for guinea pigs as well as rats.

On the other hand, Uhlenhuth and Zuelzer[2] have isolated by culture from aqueduct water a spirochaete which subsequently acquired distinctly pathogenic properties for animals. This spirochaete in doses of 2 to 4 cc. of the culture, when injected intraperitoneally produced in guinea pigs a disease which after four to eight days caused death. The entire appearance in the animals so infected corresponded with that of Weil's disease. This water spirochaete was also pathogenic for mice. Zuelzer regards this spirochaete as identical with the one which produces human Weil's disease. The cultures were made in sterile tap water to which was added 15 to 20 per cent of rabbit serum. Before being inoculated the

[1] NOGUCHI; *New York State Jour. Med.*, 1922, XXII, 426.

[2] UHLENHUTH and ZUELZER; *Central f. Bakt. u. Parasit.*, 1922-23, Orig., p. 171.

tubes were warmed for an hour at from 55°C. to 60°C., in order to inactivate the serum. By frequent inoculation from the surface of such culture the spirochaetal growth was increased. The culture of the spirochaete obtained was not pure, but was mixed with a coccus, but the coccus when injected alone into the animal produced no pathogenic changes. It is reported that with two of the water strains isolated, a potent immune serum against *Spirochaeta icterohaemorrhagiae* was made.

From these experiments and others of a similar nature, Zuelzer and Oba[1] conclude that non-parasitic, saprophytic spirochaetes may become under certain conditions pathogenic, but that such changes come about very slowly. Thus the water strain of *Leptospira icterohaemorrhagiae* which was isolated from water, it is stated only became pathogenic for guinea pigs after it had been cultivated in serum media for one and one-fourth years. Elaborate serological and biological experiments were carried out to demonstrate the identity of this strain with the natural pathogenic strain of *Leptospira icterohaemorrhagiae* of Weil's disease.* This is the most striking example reported of a free-living, saprophytic spirochaete which has gradually acquired definite pathogenic properties.

The subject of *symbiosis* and mutualism and their relationship to parasitism, because of their broad biological interest should appeal not only to the physiologist and pathologist, but to the zoölogist as well. These phenomena which have so frequently been observed among both animals and plants may affect profoundly their structure and behavior, or even their existence. The term "symbiosis" which has sometimes been misapplied in medical literature, signifies a condition of conjoint life existing between different organisms of varied or even the same species, both organisms being benefited by the partnership. Obviously a condition of perfect symbiosis with different species is very rarely if ever realized either in plants or animals, since such a condition would require that each of the organisms should render to the other an exact equivalent of what it received, and that the organisms in question should be entirely adapted to a life in common.

*More recently Buchanan has isolated a similar microörganism from mud and slime. See *British Med. Journ.*, Nov. 29, 1924, p. 990.

[1] ZUELZER and OBA; *Central f. Bakt.*, Abt. I, Orig., 1923, p. 95.

This ideal balance, even if attained, becomes frequently disturbed, and in some groups of animals sooner or later one organism becomes more dependent upon the other, and the symbiotic relationship passes into one of parasitism in which the degree of adaptation may vary greatly. Thus, the new condition may approach that of symbiosis and a mild parasitism result, or it may pass to the other extreme, one organism assuming highly pathogenic properties for the other and perhaps causing its destruction. Again, certain forms of parasites do not nourish themselves on any part of the host. They belong to the group of commensals or more correctly, according to Fantham and Stephens, of "space parasites" which simply dwell within their host and do not even take a portion of the superfluity of its food. However, the presence of such "space parasites" may be regarded as constituting the first stage of commensalism which, in turn, may again be regarded as a sort of transition stage to true parasitism.

On the other hand, in some instance it is conceivable that the symbiosis originates through a preliminary stage of parasitism on the part of one of the organisms, the struggle for supremacy ending in mutual adaptation. In either instance it is evident that there is no definite boundary between symbiosis and parasitism. As Nuttall[1] has pointed out, the factors governing immunity from symbionts or parasites are essentially the same. The condition of life defined as symbiosis may then be regarded as balancing between two extremities, complete immunity on the one hand, and deadly infective disease on the other.

Among insects there are found innumerable examples of such progressive adaptations toward an association with microörganisms of different type. Nuttall has classified symbiosis in insects into four groups: (1) the utilization by insects of microörganisms cultivated by them outside their bodies; (2) symbiotic organisms developing in the lumen of the intestine and its adnexa; (3) intestinal symbionts situated in the epithelial cells of the digestive apparatus; and (4) intracellular symbionts of deep tissues. The symbionts may be bacteria, yeasts, saccharomycetes, protista, or rickettsia.

[1] NUTTALL; *Rep. Brit. Assoc. for Adv. Science*, 1923, p. 197.

Various hypotheses have been advanced to explain the possible function of the symbionts but our knowledge of this subject is still very meagre. Even the classification of these microörganisms is sometimes difficult. Thus Buchner[1] has found symbionts in *Cimex lectularius* which live in large cells called mycetocytes or within a new symbiotic organ, the mycetome. These microörganisms he regards as bacteria. On the other hand, Arkwright, Atkin and Bacot[2] have described a similar microörganism in *Cimex* under the term *Rickettsia lectularia*. Also Jungmann[3] and Arkwright and Bacot[4] have described in the sheep louse, as stages of rickettsiae, certain forms which are regarded by Hertig and Wolbach[5] as yeasts or "yeast-like" organisms.

The recent observations of Hertig and Wolbach (loc. cit.) only serve to emphasize how much confusion there still exists regarding the forms of life so widely distributed throughout the arthropods and which have recently been referred to under this term of "*Rickettsiae*." They also demonstrate the great difficulties in the recognition of rickettsiae, some observers regarding the forms described under the term *Rickettsia* as yeasts, bacteria, symbionts or even as degenerated cell products or flagella of protozoa. While the cultivation of some of the pathogenic species of *Rickettsia* has been described, until more satisfactory methods of culture are discovered and direct inoculations made into man or susceptible animals with these pure cultures, even the etiological relationship of some forms to disease must still remain somewhat obscure.

As the writer pointed out some years ago[6] certain of the rickettsiae of *Pediculi* which are harmless to man, as was demonstrated by experiments in which such pediculi were fed on human beings, cannot be distinguished morphologically or by any other known means from the *Rickettsia* be-

[1] BUCHNER; *Tier. 9. Pflange in intracellular Symbiose*, Berlin, 1921, and *Arch. f. Protist.*, 1923, XLVI, 225.

[2] ARKWRIGHT, ATKIN, and BACOT; *Parasitology*, 1921, XIII, 27.

[3] JUNGMANN; *Deut. med. Woch.*, 1918, XLIV, 1346.

[4] ARKWRIGHT and BACOT; *Trans. Roy. Soc. Trop. Med. & Hyg.* 1921–22, XV, 146.

[5] HERTIG and WOLBACH; *Jour. Med. Research*, 1924, XLIV, 329.

[6] STRONG; Contributions to *Med. and Biol. Research* dedicated to Sir Wm. Osler, 1919, p. 1205.

lieved by some observers to be the cause of trench fever. However, there is no evidence of any of these symbionts being pathogenic for the arthropod and among the rickettsiae only *Rickettsia prowazeki* exhibits moderate pathogenicity for its insect host while the *Rickettsia* described as the cause of Rocky Mountain Spotted Fever would appear to be a harmless parasite rather than a symbiont to its insect host, the tick, (*Dermacentor venustus*). Wolbach believes that this rickettsia is probably parasitic in process of adaptation to the tick. The view recently expressed by Weigl[1] that *Rickettsia prowazeki* is merely the form assumed by *Bacillus proteus X* in the louse seems hardly tenable.

As no one has succeeded yet in cultivating on artificial media the symbionts of blood-sucking insects their true nature is also still undetermined. Florence[2] has recently studied the symbiont in the hog louse, *Haematopinus suis*, and has been able to obtain some evidence in favor of the view that it is connected with the physiology of digestion in the insect in that the location of the mycetocytes containing the symbiont is in the mid-intestine where digestion takes place; that the mechanical control of the increase of the symbiont is through the rupture of the mycetocytes; that there is careful provision for transmission of the symbiont to the next generation and an inability to raise a second generation of it when the lice are removed from their natural host and fed on man.

Wheeler[3] has recently emphasized the importance of the study of the phenomenon of symbiosis and parasitism in many species of ants and termites, and of the importance in the lives of certain termites of the existence of the numerous intestinal infusoria or flagellates. These occur only in the soldiers and workers of the termites and have been variously interpreted as parasites, commensals, and symbionts. The recent investigations of Imms[4] and of Cleveland[5] are confirmatory of the idea that these protozoa of termites are true symbionts which break down the particles of wood ingested for food and render them more easily assimilable by the

[1] WEIGL; *Zeit. f. Hyg. u. Infekt.*, 1923, XCIX, 3, p. 308; *Klin. Wochen*, 1924, III. No. 35, p. 1590.

[2] FLORENCE; *Amer. Jour. Trop. Med.*, 1924, IV, 397.

[3] WHEELER; *Social Life Among Insects*, New York, 1923.

[4] IMMS; *Proc. Roy. Soc.*, Lond., 1919, 209B, p. 75.

[5] CLEVELAND; *Biol. Bull.*, 1924, p. 179.

termites. The termites themselves, as Cleveland has shown, die in ten to twenty days if fed on wood after the protozoa have been removed from them because they cannot digest their food. On the other hand the termites do not die but live indefinitely when fed digested wood or when reinfected with protozoa and fed wood. Hence he believes that it is highly probable that the termites are dependent on the protozoa to digest their food for them.

Buscalioni and Comes state that *Trichonympha agilis*, harbored by *Reticulitermes lucifugus*, when treated with iodine dissolved in iodide of potassium, gives a characteristic glycogen reaction in a region near the nucleus, and that this reacting region is sharply defined from the rest of the body. Cutler[1] could not locate a definite glycogen reacting area in *Pseudotrichonympha pristina*, harbored by *Archotermopsis wroughtoni*, but, on the contrary, found that the glycogen reaction was diffused through the entire organism. According to Certes glycogen is present in the protoplasm of the infusoria and the latter perform a special rôle in the digestion process of certain ruminants.

In the study of parasites of termites in Brazil, numerous gregarines, flagellates, and spirochaetes were found in great abundance in the intestine. While no information was obtained as to whether these microörganisms lived symbiotically within their host, none of them seemed to affect unfavorably the life of the termites and apparently they led therein a saprophytic existence. The spirochaetes observed were particularly of two types: in the first type, the organism measured from 65 to 75μ in length and from 1 to 1.5μ in thickness. The ends were rounded. They showed seven to eight spiral turns. The second type measured from about 40 to 50μ in length, and about 1μ in thickness, the extremities being tapering and pointed. These spirochaetes seemed more motile than those of the first type. They also had from seven to eight spiral turns. These two types observed in termites in Brazil probably correspond to *Treponema termitis* (Leidy) and *Treponema minei* (Prowazek) which have recently been described particularly by Hollande.[2]

[1] CUTLER; *Quarterly Jour. Micro. Sci.*, 1921, LXV, p. 247.

[2] HOLLANDE; *Arch. Zoöl. Exp. et Gen.*, 1922, LXI, p. 23.

In continuance of our experiments with saprophytic spirochaetes, inoculations of suspensions in normal saline solution of portions of the intestinal contents of termites containing spirochaetes, were also made into white mice and guinea pigs. The inoculations were made both subcutaneously and intraperitoneally.

In the experiments in which the inoculations were made intraperitoneally into guinea pigs, drops of fluid were often withdrawn from the abdominal cavity by means of a capillary glass pipette about two hours after the inoculation, and examined under the microscope and with the dark field illumination, but no living spirochaetes were found and no evidence of the pathogenicity of these spirochaetes was obtained from either the intraperitoneal or subcutaneous inoculations into mice and guinea pigs.

The majority of the recent experiments reported, in which subcutaneous or intraperitoneal inoculation of laboratory animals such as mice and guinea pigs have been made with the *flagellates* which are found in insects, and which live an apparently saprophytic existence in them, have generally resulted negatively. Laveran and Franchini[1] reported the successful infection of mice by causing them to ingest material containing *Herpetomonas ctenocephali*, or by inoculating them subcutaneously with this flagellate, and Fantham and Porter[2] reported that young mice may be inoculated subcutaneously or fed with *Herpetomonas jaculum* from the gut of the hemipteron *Nepa cinerea*, the so-called water scorpion, with fatal results. On the other hand, Hoare[3] was unable to infect fifteen mice by intraperitoneal inoculation of *Herpetomonas jaculum*. Chatton[4] also inoculated a suspension of thirty dog fleas containing *Herpetomonas ctenocephali* intraperitoneally into two mice, but the results were negative. Noller[5] likewise only obtained negative results in the inoculation of mice with pure cultures of *Herpetomonas ctenocephali*. Recently Glaser[6] and Becker[7] were also unable

[1] LAVERAN and FRANCHINI; *Bull. Soc. Path. Exot.*, 1914, VII, 605.

[2] FANTHAM and PORTER; *Proc. Camb. Philosophical Soc.*, XVIII, p. 39.

[3] HOARE; *Parasitology*, 1921, XIII, 67.

[4] CHATTON; *Bull. Soc. Path. Exot.*, 1919, XII, 313.

[5] NOLLER; *Arch. f. Schiffs. u. Tropen.*, 1920, XXIV, 168.

[6] GLASER; *Jour. Parasitol.*, 1922, VII, 99.

[7] BECKER; *Amer. Jour. Hyg.*, 1923, III, 462.

to infect animals by subcutaneous or intraperitoneal inoculation of other species of flagellates; namely, *Herpetomonas muscae-domesticae* and *Crithidia gerridis*. Shortt[1] in extensive experiments has, in addition, failed to infect vertebrates with *Herpetomonas ctenocephali* and *Herpetomonas luciliae*. During the past year, however, two successful reports of the inoculation of mice with other flagellates of insects have been made. The first of these results was obtained by Shortt and his co-worker Swaminath[2] whose negative results with other flagellates of insects have just been referred to, and these positive results are therefore more striking. Bedbugs (*Cimex hemiptera*) were fed on cases of kala azar which showed parasites in the peripheral blood. They were dissected nine days later and the contents of the guts were suspended in saline solution and injected intraperitoneally into mice. The minimum period of nine days was chosen as it was presumed that at the ninth day all the forms present would be in the flagellate condition. Of five mice which were inoculated with the suspension of twelve to twenty of the insects' intestines, one gave a positive result on the 123d day, a culture of the flagellate being obtained from the spleen. Shortt concludes that it is thus demonstrated that nine days after feeding on a kala azar case, the intestine of bedbugs may contain flagellates of leishmania which are infective to mice.

Gaminara[3] found the Uruguayan *Triatomae* to be infected with intestinal flagellates corresponding morphologically to the developmental forms of *Schizotrypanum cruzi* in the insect. Inoculations of experimental animals with these flagellates resulted in their infection. The infected animals showed in their cardiac and skeletal muscles the typical leishmania-like forms of the parasite.

During the previous year the writer[4] has shown that a flagellate which passes one stage of its life-cycle in *Euphorbiae* and which is not pathogenic for laboratory animals when inoculated from such an environment, may after its passage from the plant through its insect and vertebrate hosts,

[1] SHORTT; *Indian Jour. Med. Res.*, 1923, X, 908.

[2] SHORTT and SWAMINATH; *Indian Jour. Med. Res.*, 1924, XI, 965.

[3] GAMINARA; *Anales de la Fac. de Med. Montevideo*, 1923, VIII, 311.

[4] STRONG; *Amer. Trop. Jour. Med.*, 1924, IV, 345.

acquire pathogenic properties for monkeys.* This is apparently another striking example of a microörganism which in its adaptation to changed environment gradually acquires pathogenic properties. The effect of environment upon species in all forms of life both in suppressing or bringing inherent potentialities to expression, seems unquestionable, and either physiological or morphological changes may be developed in a parasite as a result of exposure to altered environment.

Even with lower forms of life, the bacteria, we are cognizant of examples of somewhat similar phenomenon. Thus Courmont and Rochaix[1] have found, as have other investigators previously, that by frequent subculture of the four types of bacillary dysentery bacilli on the same sugar media, they come in time to acquire the power of splitting that particular carbohydrate. One generation of organism can be trained to ferment a sugar to which it is unaccustomed. While this property lasted usually only for that generation and could not be transmitted to the next, there were certain exceptions to the rule.

D'Hérelle[2] reported that under the influence of his bacteriophage it was possible to produce secondary races from the original Shiga strain of the dysentery bacillus which differed mainly in their power of fermenting certain sugars.

Busson and Ogata[3] have very recently reported experiments, using eleven strains, of Shiga, Strong, Flexner, and Schmitz types of dysentery bacilli and three bacteriophages. By injecting rabbits with a mixture of original strains which had been acted upon in a typical manner by the bacteriophage, agglutinating sera were prepared. The sera thus prepared were tested against the original and secondary strains. By these means it was shown that the secondary races were no longer agglutinated by the original serum. The authors believe that the secondary races are divisible into two types: those which permanently retain the newly acquired properties, and those which do not.

* A large amount of the experimental work on which these conclusions are based was performed in the Laboratories of the United Fruit Company in Tela, Honduras.

[1] COURMONT and ROCHAIX; *Jour. Physiol. et Path. Generale*, 1924, XXII, 377.

[2] D'HÉRELLE; "Le Bactériophage" *Monographies de l'Institut Pasteur*, 1921.

[3] BUSSON and OGATA; *Wien. Klin. Woch.*, 1924, XXXVII, 665.

Fejgin[1] also found that the dysentery bacillus under the influence of its lytic bacteriophage substance, produced a new race differing both in serological and biochemical properties from the original strain of Shiga's bacillus.

Reference has been made to the fact that animals even as high in the scale of life as insects, find it difficult or impossible to digest crude cellulose. In this connection Imms[2] has pointed out that the symbiosis between the intestinal protozoa and the termites is paralleled by the occurrence of numerous genera of *infusoria* in the stomachs of ruminants, notably of the ox, sheep, goat, camel, and reindeer. It is believed that by means of their action upon the vegetable matter consumed by the ruminants these infusoria help to render it capable of being digested by the latter. These infusoria are absent from the stomachs of the young ruminants prior to being weaned from their parents. According to Certes, glycogen is present in the protoplasm of the infusoria and the latter perform a special rôle in the digestive process of the ruminants. Gruby and Delafond maintained that the protoplasm of the infusoria is itself digested and thereby contributes towards the nutrition of the host ruminant. Similarly, the infusoria inhabiting the large intestine of the Equidae, Imms states, are possibly symbiotic in their relations with their host. Whether a true symbiosis exists in a number of these instances seems questionable. It is true that the ciliated infusorium, *Balantidium coli*, lives commonly in the normal intestine of pigs apparently as a harmless commensal. There is no evidence in favor of or contrary to the fact that it lives in symbiosis with its host. Glaessner has reported the isolation of a diastase and a haemolysin, but no proteolytic ferment has been yet isolated. It is also not known that it plays any special rôle in the digestive process of the pig. However, when this infusorium lives in the large intestine of man or in orangutans, under certain conditions which we cannot explain, it assumes pathogenic properties and invades the tissue, giving rise to an ulcerative form of dysentery[3] which, especially in orangutans, may result fatally.

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[1] FEJGIN; *Compt. Rend. Soc. Biol.*, 1923, LXXXIX, 1381.

[2] IMMS; *Philosophical Trans. Roy. Soc.* London, 1919, 209B, pp. 75–180.

[3] STRONG; *The Clinical and Pathological Significance of B. coli.* Bureau of Govt. Lab., Bull. No. 26, Manila, 1904.

The majority of protozoölogists who have studied the question have come to believe that the *amoebae* which are found living in certain of the water supplies of tropical and subtropical countries are saprophytic and of the free-living type[1]. Dobell[2] has insisted that the dysentery amoeba (*Entamoeba histolytica*) cannot live and multiply outside of its human host, and that it must always live at the expense of its host's tissues.

However, the recent investigations of Cutler[3] and particularly of Boeck[4], who have both been able to cultivate *Entamoeba histolytica* in artificial media consisting of Ringer's solution, serum, and egg media, obviously refute these assertions by Dobell that *Entamoeba histolytica* cannot live and multiply outside of the human intestine.

As early as 1904 Musgrave[5] reported experiments in which cultures of saprophytic amoebae from hydrant water which were made upon a media containing merely agar, sodium chloride, and extract of beef, were fed to monkeys and produced amoebic dysentery in three of these animals. Another culture made on this same medium which was obtained from lettuce after the fourth washing in distilled water, was fed to a monkey and produced amoebic dysentery in the animal, while another culture of the same amoeba when injected into the liver of a monkey produced amoebic liver abscess.

Franchini[6] has recently reported the production of liver abscess in two white mice out of a series of nine which were inoculated intraperitoneally with a culture of an amoeba isolated from latex of *Euphorbia*. However, these results have not been confirmed.

The cultures of *Entamoeba histolytica* obtained by Cutler and Boeck (loc. cit.) contained amoebae associated with

[1] STRONG; *Billings-Forchheimer's System of Medicine*, 1924, III, 428.

[2] DOBELL; *The Amoebae Living in Man*, London, 1919.

[3] CUTLER; *Jour. Path. & Bact.*, 1918, XXII, 22.

[4] BOECK; *Proc. Amer. Soc. Trop. Med.*, 1924.

[5] MUSGRAVE; *Publications of Biol. Lab.*, Bureau of Science, Manila, 1904.

[6] FRANCHINI; *Bull. Soc. Path. Exot.*, 1923, XVI, 162.

bacteria. Musgrave, Lesage, Gauducheau[1], and others also cultivated amoebae together with bacteria. All of these amoebae were considered by the authors who reported the observations, to be pathogenic under certain circumstances. It has often been suggested that bacteria are necessary for the growth and multiplication of amoebae and that a symbiotic relationship exists between the amoebae and associated bacteria. Such a symbiosis, however, has not yet been satisfactorily demonstrated. However, it is well known that amoebae may exist in the intestine of man and, under certain circumstances, produce no lesions and no symptoms of intestinal disturbance. While under other circumstances, in association with these same amoebae, symptoms of dysentery and ulcerative lesions of the intestine result. Whether such a change in pathogenesis is inherent in or is developed in the amoebae is unknown. Possibly the presence and action of some lytic substance, perhaps even formed by the host, and either acting primarily upon the amoebae or upon the intestinal walls, may give rise to the production of the dysenteric symptoms and ulcerations of the intestine. Could a bacteriophagic agent exert such changes? Gauducheau believes that *Endolymax phagocytodes* is a parasitic species of the intestine of man and constitutes a form of passage between the *Entamoebae* which are culturable with difficulty and the free-living amoebae.

SUMMARY

Among the nematodes a number of examples occur in which parasitic species have gradually developed from free-living forms, and in some instances nature in her desire to successfully perpetuate the species has provided for both the parasite free-living and parasitic generations, as is strikingly illustrated in *Strongyloides intestinalis*. In the case of *Aphelenchus*, a small nematode which gives rise in association with other microörganisms to the "red ring" disease of the cocoanut palm, the development of parasitism from the free-living forms of the nematode has been in the direction of plant rather than of animal life.

Certain saprophytic microörganisms (spirochaetes associ-

[1] GAUDUCHEAU; *Bull. Soc. Path. Exot.*, 1922, XV, 229.

ated with fusiform bacillary forms) are found in the normal mouth or tonsils or on the genital organs of many individuals. Under certain circumstances in which the resistance of the individual is lowered, and the tissues subsequently bruised, burned, or otherwise injured, these microörganisms may by mutation and adaptation gradually develop pathogenic properties and produce extensive ulcerative and even gangrenous lesions. Such ulcerations may occur about the mouth and throat, in the lungs, about the genital organs, and, particularly in the tropics, upon the legs where large chronic ulcerations often result. While similar spirochaetal microörganisms occur sometimes in the intestinal tract of individuals, their exact relationship to intestinal disease is still obscure. It has been suggested that they may under some circumstances give rise to dysenteric symptoms, or in other circumstances to chronic gangrenous appendicitis.

The free-living spirochaetes of water have generally been considered as saprophytic or harmless microörganisms, but recently there have been found in certain stagnant waters, or on the surface of filters, a number of spirochaetes which correspond morphologically with the parasitic species such as *Treponema pallidum* of syphilis, *Leptospira icterohaemorrhagiae* of Weil's disease, *Spirillum obermeieri* of relapsing fever, and *Spirochaeta hebdomadis* of seven-day fever. From some of these waters a spirochaete has been isolated which not only corresponds morphologically to the organism of haemorrhagic jaundice or Weil's disease, but which after long cultivation in serum media, may acquire disease-producing qualities and give rise, on inoculation into animals, to typical haemorrhagic jaundice, the infection frequently resulting fatally to the animal. This is a most striking example of a free-living saprophytic spirochaete which has gradually acquired definite pathogenic properties.

Our knowledge of the development of pathogenic and parasitic properties of symbionts and rickettsiae found so commonly in many insects, is still in a very confused state, and until pure cultures of these are obtained which can be made practical use of, the relationship of most of these forms to disease must still remain doubtful.

The majority of the recent experiments reported, in which attempts have been made to infect laboratory animals with

the flagellate parasites found in insects, and which live an apparently saprophytic existence in them, have generally resulted negatively. However, it has more recently been demonstrated that when mice are inoculated with flagellates in the intestinal contents of bedbugs, which insects have previously fed on a patient suffering with kala azar (black sickness of India), infection of the animal may result. Laboratory animals have also recently been successfully infected with the parasite of South American sleeping sickness by inoculating them directly with the flagellates from the intestinal contents of a *Triatoma* (a species of kissing bug).

Another striking example of a microörganism which in its adaptation to changed environment gradually acquires pathogenic properties, is seen in the case of *Leptomonas davidi*. This flagellate which passes one stage of its life-cycle in the plant *Euphorbia*, and which is not pathogenic for laboratory animals when inoculated from such an environment, may after its passage from the plant through its insect and vertebrate host, the lizard, acquire definite pathogenic properties for monkeys.

The development of parasitism and pathogenicity by certain amoebae and infusoria which previously led a saprophytic existence is still unsatisfactorily explained. The pathogenic amoebae cannot be cultivated in artificial media with the same facility as the free-living forms.

DISEASE RECORDS AS AN INDISPENSABLE MEANS OF DISEASE PREVENTION

Arthur Newsholme, M.D.

The subject on which I am asked to address this Conference forms a chief corner-stone on which efforts for the prevention of disease are built; for the history of public-health progress in the older countries is bound up with increasing knowledge of the prevalence of disease and of its distribution. This knowledge is only secondary in importance to accurate knowledge of the causal agents of disease; and when the causal agent of a given disease is known, and its method of attack has been accurately ascertained, knowledge of the incidence of the disease is indispensable for preventive action. It was statistics of the incidence of "fever" in England, in the early forties of the 19th century, which impelled the adoption of the important English sanitary reforms, and their sequential adoption in all quarters of the world.

Theoretically, it might be considered possible to reduce the incidence of a preventible desease in the absence of exact knowledge of its presence, its amount and its local distribution.

Thus the life history of tropical diseases like malaria and yellow fever, cholera, enteric fever, and smallpox being known, one might proceed to act, so to speak, *in vacuo* without knowledge of individual cases of these diseases, as by instituting measures for the draining or sterilization of marshes and the destruction of anopheles (malaria and yellow fever); for compulsory vaccination against smallpox; for the provision of clean water supplies (cholera and enteric fever); for the installation of satisfactory privy accommodation for every household (ankylostomiasis, etc.); and so on.

But experience shows that such action on the strength of scientific knowledge, apart from the pressure of a known evil, is seldom effective and continuous; the most efficient spur to action is the disagreeably obtrusive notification of each case of disease and its official record in reports published at short intervals.

This is true even when the exact natural history of each disease has not been worked out. It is a noteworthy fact in the history of disease-prevention in England that a large share of the phenomenal reduction in enteric fever was secured before the Eberth bacillus was known, and much of it also before the close association of the major typhoid epidemics with water-pollution was ascertained. The crude and imperfect generalisation that excremental filth meant disease, had been reached; and on the basis of this, active and successful efforts were made for the removal of nuisances — including all accumulations of organic filth — which incidentally meant also the freeing of water supplies from their main sources of contamination.

After these activities, cholera ceased to be a source of excessive alarm when occasionally re-introduced into England, and enteric fever was greatly reduced. These things were done under the stimulus of the death returns published weekly for London and some large towns. When at a later period each known case was notified, more accurate epidemiological inquiries became possible, and so milk and shell-fish as frequent sources of disease were discovered. At a later stage bacteriological science rendered possible an even more rigid determination of a source of danger not previously suspected, viz. "carrier cases;" and through the coördination of these various preventive factors, enteric fever promises ere long to become as rare as typhus fever, which in Western Europe is almost extinct in times of peace.

Typhus fever is interesting as an example of the almost complete disappearance of a disease, so far as Great Britain is concerned, although a knowledge of its specific bacterial origin is an event of only yesterday. Its disappearance, furthermore, has been secured through efforts,— including hospital segregation of cases, surveillance of contacts and cleansing of premises and of bedding and apparel — not specifically directed toward the killing of lice, which probably are the sole vectors of infection. In this disease measures for preventing infection (segregation of cases and disinfection of articles) were successful, once the cases became known although the special means by which infection spread remained unknown. How much more rapid might the decline of typhus have been, had the importance of "delousing" been discovered earlier?

In no instance has striking reduction of a disease, such as is illustrated above, been secured without knowledge of its general incidence. The case of tuberculosis perhaps may be adduced to the contrary. But this disease always and everywhere persistently advertises its presence, and calls for social treatment; and it is under the influence of the cleanlier habits of patients, of the extensive hospitalisation of a high proportion of bed-ridden cases, as well as of the diminution and removal of the provocative agents which bring latent tuberculosis into activity, that this disease has become not more than half as serious a cause of mortality as it was a generation ago.

We may assert generally, as an axiom in sanitary practice, that the pointer to prevention has always been the occurrence of disease. In this, as in so many other aspects of life, the sufferings of the sick are the vicarious means of reducing and abolishing the sufferings of others. The vicarious principle runs through life.

Dr. W. H. Frost and his co-workers in Maryland have found that in country villages the careful ascertainment of the local incidence of enteric fever, over a series of years, enables concentrations of the disease to be localized; carrier cases or other sources of infection are revealed; and thus action effective in diminishing disease can be more rapidly secured than by the adoption of a general system of anti-typhoid inoculation or by the relatively slow process of general sanitation.

The necessity of knowledge of each case of such diseases as smallpox, cholera, leprosy, ankylostomiasis, need not be specially urged.

In tropical regions evidently the difficulties in ascertaining the occurrence of disease are exceptionally great. There may be no complete registration of deaths and their causes; and except on plantations on which good organization prevails, including the provision of medical attendance for every employe, notification of cases of infectious diseases is likely to be very incomplete. The desiderata are:

(1) A statement of the population at risk, distributed according to sex, and if practicable in age groups.

(2) A record of the number of births occurring in each locality, as without this a completely trustworthy statement of infant mortality cannot be made.

(3) A record of the number of deaths, the cause of death, if possible, being medically certified.

By means of such complete records, year by year, the main conditions of the healthfulness of a district or a plantation can be gauged.

But for current and prompt intervention, with a view to the prevention of further mischief, such returns are inadequate. They are valuable historically; and they may make possible some preventive action, though belated.

For efficiently prompt action, immediate notification of each case of preventible sickness to a responsible medical officer is required. The importance of such notifications need scarcely be stressed. Past experience has repeatedly demonstrated that it is essential for good preventive work. In the absence of a complete system of notification of all cases, much valuable administrative action can be taken on the strength of information as to cases treated in hospitals or at dispensaries, these being regarded as the starting-point for further epidemiological investigation.

Each notification of a case is a pointer. It shows a centre of infection. Even in well-organized areas, notification of cases is seldom complete; and notification of cases has relatively small value *unless each case is regarded as the starting point of an epidemiological investigation* with a view to the discovery of overlooked or concealed cases. This is particularly so in smallpox; but the same rule applies, for instance, in ankylostomiasis. When a case of this disease has been medically recognised, only the minimum amount of good has been done when the patient is placed under treatment, unless the condition of the patient's family and co-workers, as regards ankylostomiasis, has been ascertained, and any detected cases have been brought under treatment, and prophylactic measures adopted for all alike.

This means the carrying out of "field work" in connection with the clinical treatment of every ascertained case of a communicable disease, whether chronic, like syphilis, tuberculosis, leprosy; subacute, like malaria; or acute, like enteric fever, smallpox, cholera.

Such field work is an essential element, *the essential element in the practice of preventive medicine.*

It is by means of such field work that incomplete death

returns and sickness returns can be made to give their maximum results; and it is the failure to realise the importance of this field-work that prevents public-health administrators from securing the reduction of disease to the extent which is practicable.

I do not wish to minimize the importance of the laboratory investigation of disease. It is an indispensable auxiliary, especially on the clinical side of disease. On the preventive side, it is arguable whether — through no fault of the laboratory investigation, but owing to the short-sightedness of the health officer or physician — it may have lost more lives than it has saved. How many cases of diphtheria have proved fatal, owing to the failure of the physician to give antitoxin, until Klebs-Loeffler bacilli have been found in the secretions of the throat? Again and again preventive means against the further spread of cholera or enteric fever have been seriously delayed, and epidemics have been allowed to swell to unnecessarily large proportions, because of lack of prompt action on epidemiological "field" facts as to suspected water, pending the receipt of the results of chemical and bacteriological examination of this water. It is forgotten that such an examination may give doubtful results, that it may confirm suspicions but cannot justify the absence of suspicion; and that a careful epidemiological inquiry into every reported case and its possible sources of infection, followed by a collation of the facts respecting all cases, and a corresponding investigation of unnotified cases which have been searched out, is the main line of usefulness in the investigation of infectious disease, and the chief guide to sound action in the interest of the public health.

Investigation on these lines implies accurate clinical knowledge of disease. In past experience fully competent clinical skill has been found to be the best foundation for public-health practice, although it needs to be supplemented by training in the science and practice of preventive medicine.

Field investigation furthermore implies a willingness to use intelligence and the taking of unlimited pains. The accurate ascertainment of every available fact respecting every known case of infectious disease, is the indispensable preliminary to successful preventive action. To talk about

the work does not suffice; to have an excellent office plan of operations, looking most promising when shown as a scheme on the office wall, is totally inadequate. Accurate field inquiries must be undertaken, and action is never satisfactory which is not based on the correlated facts ascertained by an intelligent study of these field observations. No source of information, no instrument of inquiry, clinical, epidemiological, or laboratorial, is to be neglected, as it is by the balanced and duly coördinated help of all these branches of enlightenment, that the most complete measures for the annihilation of disease become practicable.

Discussion

Sir Thomas Oliver (*Opening the Discussion*).— I have very little knowledge of this subject, but I should like to ask Sir Arthur Newsholme whether he can in any way explain the particular facts to which he drew attention, that long before the discovery of the tubercle bacillus by Koch the incidence of tuberculosis had been declining all over the world; that before the discovery of Eberth's bacillus, typhoid fever had been undergoing a similar decline; and that long before the real cause of typhus fever had been discovered, typhus fever had also declined. Now it is just these facts that place a great deal of power in the hands of the people in Great Britain, who at the present time are arguing against the use of vaccination as a preventive of smallpox. They maintain that it is not necessary to vaccinate the children at all, for, do what you like, the incidence of smallpox is declining and there is nothing like the mortality that there used to be. It is a strange fact, as Sir Arthur has pointed out, that before the real causes of these diseases had been discovered their incidence had been declining.

Sir Arthur is quite right in insisting upon the value of bacteriological work. He alluded to the necessity of greater coöperation between the ordinary medical attendant and the medical officer of health. He went on further to speak of the advisability and the advantages, which Dr. Hoffman confirmed, of coöperation between the bacteriologist and the medical profession. One would like to see, in the investigation of these diseases, still greater cooperation between the physician in attendance upon the case, and the bacteriological department. My own feeling is — and I express it with reservation — that the bacteriologists do not come sufficiently into contact with the clinical side of disease. I feel sure that if there could be brought about greater coöperation of the

bacteriological department with the clinical wards of the hospital, more rapid advances would be made. I congratulate Sir Arthur Newsholme upon the manner in which he has drawn attention to the need of a greater coöperation on the lines indicated and of the value of group-work.

Major G. C. Dunham.— I wish to congratulate Sir Arthur Newsholme on the excellent presentation of his paper, particularly on the point which he made regarding the necessity of field work in the prevention of disease.

In the Army we have found that it is absolutely impossible for one to practise preventive medicine from an office desk. It is necessary for the individual to go out into the field and actually observe the conditions themselves. Another point Sir Arthur mentioned was that the morbidity statistics serve as a pointer to indicate the existence of infections. What to my mind is equally important is, that these statistical data also serve to measure the results of preventive measures.

A point that Sir Thomas Oliver brought out, about the need of a laboratory worker's being conversant with the clinical facts, has long been recognized. We try to have our laboratory workers serve as consultants with the clinical men. Further, we endeavor to place a young man in the laboratory for a period of service, and later transfer him either to internal medicine or to preventive medicine.

The Army has compiled morbidity statistics, with only two interruptions since 1819. We had one interruption in 1830, and another at the time of the Mexican War. The morbidity and mortality statistics of the World War are now in press.

We have found great difficulty in comparing our morbidity statistics with the mortality statistics collected by the Census Bureau. There is no need to go into a lengthy discussion of the classification employed, but the international classification of the causes of death has not always given a true picture of the existing morbidity conditions, because, whereas a man dies from one disease, he may have several others as well.

Dr. Wm. H. Park.— Sir Arthur Newsholme spoke of the fact that dependence on laboratory findings sometimes costs more in lives than in remitting such dependence. I think that he really meant that clinicians often insist upon depending upon laboratory results when laboratory men themselves are the last ones to advise it; thus no laboratory man would suggest awaiting the result from a diphtheria culture before giving antitoxin. He above all others realizes the necessity of giving promptly antitoxin in any case in which the disease is at all serious. Just as it would be very wise for laboratory men to have some knowledge of clinical medicine,

so it would also be wise for clinical men and for health administrators to have some knowledge of bacteriological work. Each specialist needs some real knowledge of the other branches of preventive medicine in order to obtain the full value from assistance from such sources.

Sir Leonard Rogers.— He remarked that the extensive statistics published yearly in the annual reports of the Sanitary Commissioner with the Government of India, for over 50 years contained very valuable and reliable figures regarding the incidence of disease in the British and Indian armies; less accurate, but still valuable, figures relating to the population of Indian jails; and very inaccurate data regarding the general population; while the Provincial Sanitary reports recorded similar inaccurate data regarding the mortalities from a few of the principal diseases in different parts of India reported by uneducated village officials. Nevertheless, these figures, he said, have a relative value, and as plague, cholera and malaria have different seasonal prevalence, the total death rates give a considerable amount of information regarding the prevalence of the principal diseases if curves are plotted out. He had been able to demonstrate the spread of the epidemic of kala-azar up to Assam valley, by making out curves of the total fever mortalities, and the local appearance of the disease could be detected by examining the data for smaller areas,— proof that even these inaccurate figures had considerable epidemiological value.

Dr. F. L. Hoffman.— The question has been raised as to the underlying causes accountable for the decline in smallpox, typhoid fever and tuberculosis previous to the introduction of modern preventive measures and sanitary reforms. I think we must rid ourselves of the illusion that any one single cause is responsible for the wide-spread occurrence of the diseases to which I have referred.

Smallpox declined, not primarily because of vaccination, but because of the growth of sanitary habits on the part of vast numbers of the population. Typhoid fever declined because of the gradual introduction of modern water-supplies, without reference to the causative factor responsible for typhoid-fever occurrence. Tuberculosis has declined chiefly because of higher wages, yielding better nutrition, shorter hours yielding more leisure time and lessening fatigue, and wide-spread improvements in factory hygiene. All this does not minimize the results of deliberate efforts at prevention, but it partly explains why these diseases declined before such measures became widely effective.

Major Dunham has called attention to the confusion of our disease nomenclature. The census office has within recent years

published an admirable classification, useful for practical purposes. It should be self-evident that a nomenclature of causes of death cannot meet the situation, since very many diseases do not lead to a fatal termination. It is most desirable, however, that there should be an international agreement on this question, as there has been with reference to the international classification of causes of death.

Dr. C. A. Kofoid.— An interesting confirmation of the value of field work in locating the source of an epidemic is well illustrated in the case of a typhoid-carrier detected by the California State Board of Health. A series of unexplained outbreaks of typhoid fever among sailors on lumber schooners, on the Western Coast of the United States, led to this investigation, and also to the detection of a single sailor who had moved from ship to ship and left behind him a trail of disease and death. He was a typhoid-carrier, and he alone was the source of these recurrent outbreaks on different ships and in different ports.

The fact that human amœbiasis can be acquired only by the ingestion of the cysts of the amœbæ — which are found only in human fæces, and are derived mainly, if not wholly, from chronic or carrier cases — raises the question as to whether or not amœbiasis should be a reportable disease. It also raises the very interesting question as to whether or not infected persons should be so treated by the physician as to protect the families of the infected person and the community against further spread of the infection.

Dr. Henry Rose Carter.— I think that all that has been said on this subject, so far, is of general, or rather of universal, applicability, and not applicable to the Tropics more than elsewhere. Might it interest you to know something of how such records are, and have been, kept in the Tropics, or at least in the American Tropics?

I assisted Dr. Juan Guiteras, who is a master in this line, in 1916 in the examination of the mortuary statistics of a number of cities of South America: Baranquilla, Caracas, Bahia, Forteleza, and Pernambuco, among others. Since then I have examined by myself those of a few others. These examinations were as much to determine what had occurred in the past, as to ascertain the condition of health of the city in question at the time of examination — or rather, this last could be determined only if the first were known. The examinations then extended back some time: in the case of Baranquilla, to 12 years before, and further back than that at Forteleza.

These records —"*Libros de Defunccione*s"— were extremely well kept, clear and formal with few erasures, interlineations, or omis-

sions of data, and the books themselves were well preserved. They have been thus kept for a long time. I had no difficulty last year in getting from Havana the number of deaths from Havana for the 5 years centering on 1620, together with the census for that year. These records in all such Latin-American cities as I have had a chance to examine, are well recorded and carefully protected, although I am told that the ants have injured certain of them in Mexico. As Guiteras said: "We can rely on these entries, all except the diagnoses." These are frequently indefinite: "*fiebre*," "*calentura*" or even "*es muerto*" ("is dead")—a conservative statement certainly, if not a specially informative one.

I think that clerk, priest and custodian have done their parts by these records — and done them well — the only failure being omission of the entry which should have been filled out by our own profession. In very many cases the "cause of death" bore no evidence of having been supplied by a physician. We saw a record of 1,014 deaths as occurring in *one day* in the little town of Forteleza in Brazil — mainly from small-pox engrafted on starvation from a severe drought in the State of Ceara.

Sir Arthur Newsholme (*Closing the Discussion of His Own Paper*). — I do not know that any important points require answer, but I should like to offer Dr. Kofoid my thanks for the points which he has brought out.

I was not dealing so much in my paper with statistics, but with what — for lack of a better word — may be called sub-statistics, i.e., statistics in the rough, in the making, with which in actual practice of epidemiological work one has to deal. Before these have reached a magnitude adequate to be classed in tabular form, it is often necessary to take preventive measures. One has to act on suspicion. The main point I desired to emphasize was that each individual case was to be regarded as a link and that the other links were to be sought out by careful field investigation, while tabulation belonged to a stage which, if work was successful, might never be reached.

I am in entire sympathy with Dr. Park's remarks, and am glad to have elicited them. I was not reflecting on the laboratory investigator. I was reflecting on those health officers, and still more on those private physicians, who misuse the opportunity of laboratory investigation which has been given to them.

In regard to Sir Thomas Oliver's questions, I am glad he emphasized the point which had been brought out in my paper respecting 3 important diseases — tuberculosis, typhus fever and typhoid fever — viz., that they had declined, apart from exact knowledge of their causal organisms. There can be no doubt that the removal of filth from dwellings, with the purifying of the water supply, was the main cause of eradication of typhoid fever.

The causes of decline of tuberculosis are much more open to difference of opinion, but there can be no doubt that there were social factors at work which not only were improving the resistance of the population to infection, but were also diminishing infection. The influence of housing on tuberculosis was mentioned, and that is of supreme importance, but there is still a very inadequate realization of the fact that, while more people are living in towns in crowded conditions, housing has been improved to an enormous extent by providing additional hospital beds for the sick.

The statistics of all great cities, and of most countries, show that in the last 40 or 50 years the proportion of sick people who have been treated in hospitals has been rapidly increasing. In London between 50 and 60% of the deaths from tuberculosis occurred in the city hospitals, and the same is true of New York City and other large ports. In other words, the stress of the housing situation has been diminished and the risks of over-crowding reduced by removing the sick for hospital treatment. That is one of the important factors to be brought under consideration.

I think those are the main points which have received any discussion, and I merely repeat what I set out to say, that I am confident that in the prevention of disease the most important single item is to regard every case of illness as a center from which to ascertain other cases.

Truxillo Railroad Hospital at Puerto Castilla, Honduras

THE NEEDS OF PUBLICATION IN TROPICAL MEDICINE

HENRY J. NICHOLS, M.D.

A critical survey of all the publications in the world devoted to tropical medicine would be an attractive and desirable achievement, but it is more of a project than I can undertake at present, and instead a few observations are submitted on the records of the English-speaking countries. These records are, of course, only a small part of the expression of creative racial energies in our civilization as a whole. They are of great significance, however, because many social, as well as individual, failures in the Tropics have been due to the neglect or lack of scientific medicine while many successes can be credited to its cultivation.

Practically all our special records in tropical medicine have been born in the last thirty years. In other words, we are in the midst of a movement, and cannot fully appreciate just what is going on. The message of science, however, is that man's life on this globe is more or less in his own hands, and it is interesting to see, if possible, in what direction we are traveling.

In view of the proved economic value of scientific medicine in the Tropics, it might be thought that adequate avenues of expression would be provided. It might be thought that the recording of the precious workings of consciousness would be a first consideration. Such, however, is not always the case. While a good deal has been done along these lines, too often immediate results and financial and administrative factors are given precedence. Scientific records are apt to be the last to be established and the first to feel the cut of economy. For example, I understand that it has been stated that scientific medical records were not essential for the operation of the Panama Canal, and they have suffered accordingly. Again, when a study has been made, an author often has difficulty in placing his work. If finally placed, it may be delayed many months in pub-

lication, and the author may have to share the expense. Many publications are operating on a slender margin, and editors have a difficult time between pressure for reduction of expenses, on the one hand, and on the other the demands of the subject for adequate and dignified expression.

What is to be said about this situation? If scientific medicine is really so valuable in tropical civilization, its fruits should be guarded and treasured.

Of course, scientific publication, like everything else, must in a measure make its own way in the struggling world. There is a healthful and saving element in the struggle for existence, but it should not be necessary to fight over the same ground indefinitely. Now that the scientific approach has proved its value and possibilities, it should be made easier rather than be obstructed.

In surveying the situation, we come sooner or later to the responsibility of the individual worker. Before asking the world to accept our currency, we should see to it that it has a par value. There is a constant need for the self-criticism and self-discipline which Pasteur so often insisted on. Scientific work has now a certain place, but many workers abuse the privileges of their position. They string their stories out to an unconscionable length. They take side trips up blind alleys and substitute egotism and personal idiosyncrasy for the serious and noble ideals of conscious effort. In recording scientific work, it is impossible to make a cinematograph of every move in the laboratory, or at the bedside, or in the operating room. The world may justly demand that the worker furnish only the really valuable and significant products and that the wastebasket be duly patronized.

Granting that some struggle for existence is desirable, and that the individual worker plays the game fairly, what can reasonably be expected in this field of human endeavor? A brief survey of existing means of publication will bring out some of the possibilities.

Records of tropical medicine can be classified as follows:

1. *Articles in general journals or publications.*— Some of Ross's first work was reported in "The Lancet" and in the British Medical Journal, and Reed's first report was in the Proceedings of the American Public Health Association. Of

course, any general journal is willing and eager to publish important papers from any field of medicine, but the significance of some work is not always apparent at first, and much solid work has no general appeal. The editor of a general journal cannot be expected to give much space to exotic subjects. There are, of course, some general journals published in the Tropics or Sub-Tropics which help the situation. The drawback to these journals is that they are apt to be local in circulation, and therefore to have a somewhat limited if not a precarious existence.

2. *Special journals*, which may be sub-divided into:
   1. Popular journals.
   2. Research journals.

The best all-round journal is the Journal of Tropical Medicine and Hygiene, founded in August, 1898, as a monthly, and now published as a bi-weekly. It had its struggles at first, but now seems well-established. It contains editorials, personal notes, and some reviews, as well as regular articles. This journal has for years been a welcome arrival to many physicians in the Tropics. A counterpart in American literature would be desirable.

Most of the journals, such as the Annals of Tropical Medicine, the Indian Journal of Medical Research, the Philippine Journal of Science and the American Journal of Tropical Medicine, can be called research journals in the sense that they present chiefly studies of subjects, rather than clinical experiences, and contain little or no personal matter, editorials or reviews. The subject of reviews will be taken up later, but it is believed there is a place, even in these journals, for personal notes and for occasional editorials.

Efficiency and progress depend on specialization, and specialists require some medium of expression. This is best secured through special publications. The stimulating effect of special journals is well known. But, of course, there is a limit to the support of such publications, and one of the great troubles of the present is that there are so many special journals struggling to exist in various fields of medicine that they overlap and compete with each other, and eventually some of them have to drop out. Some 1,900 journals are received each year at the Army Medical Library. This is a larger number than would be allowed as necessary

by a super-censor of scientific matters. The field of tropical medicine is large enough to support certain media of expression, but not large enough for much competition. Coöperation rather than competition is needed, with specialization within the fields. By a "gentleman's agreement," or otherwise, certain kinds of work should appear in certain kinds of publications.

3. *Reports of organizations*, like the Isthmian Canal Commission and the United Fruit Company, which contain much valuable material mixed in with other matter of less general interest. If these publications are to have the best standing as professional publications, the scientific material should not be buried with administrative and statistical matters, but should be dignified, as in the latest report of the United Fruit Company, by a separate section, and in many instances summaries should be published in standard journals. Attempts to curtail these publications, like the recent one in the Canal Zone, should be resisted with all our influence. Once started, these reports become indexes of progress and afford an important means of yearly comparison which should by all means be perpetuated.

4. *Government reports.*— Some government reports, such as those of India, are standard scientific publications and are issued in suitable form. More often, however, scientific data are effectively concealed in a husk of routine matter. Another way of burying data is to put them in a confidential report. Other reports are so inconclusive that they are appropriately buried in the files. Anything of significance should be brought out into the daylight of current information, either in an established series of scientific reports, or in recognized scientific journals.

5. *Bulletins of institutions and schools*, like those of the Wellcome Research Laboratories, the Liverpool School of Tropical Medicine, etc.

These can be classed as standard publications, and members of the staffs of these institutions are fortunate in such facilities. But many series of bulletins have come to an untimely end and remain dumbly on library shelves, like the blind ends of extinct lines in charts of organic evolution. Scientific medicine has a survival value in our civilization which should be reflected in our records.

6. *Proceedings of the societies, congresses and conferences.* — These serve a most useful purpose. The proceedings of the Royal Society of Tropical Medicine are a model of interest and of technique of publication. The records of congresses and conferences are mines of information, if sufficiently distributed and not too long delayed. The plans for the record of this unique Conference, with its verbatim report of its sessions, show the fullest realization of the title of this paper.

7. *The material scattered about in the various publications* which have just been roughly outlined evidently needs to be brought to a common focus. This is wonderfully accomplished by the *Bulletin of the Tropical Diseases Bureau.* It is difficult to praise this publication too highly. Practically every written record is reviewed, and in addition the reviewers often give a critical opinion of the work. This seems to me a much-needed feature in abstracts, but one seldom attempted. Of course, it can be abused, but a fair criticism by a competent reviewer would help keep our records straight. The editors are to be congratulated on this work. Another most valuable feature is the summaries which are given in each subject, at intervals, by experienced workers. Altogether this abstract journal is all that could be hoped for, and makes the ordinary fragmentary review section seem inadequate. This bulletin cannot be competed with, nor dispensed with. "The Referate" of the German Centralblatts attempt something of the same kind, but it is questionable if they can reach again the position they held before the War.

8. *Some mention should be made of books.*— This field is very well covered for general use by Manson's classical work and Stitt's condensed manual. For reference, we have Castellani and Chalmers' encyclopedic work, and Archibald and Byam's "System." The cost of the latter work, however, about $60.00, suggests some of the difficulties which editors and publishers face in covering this field. There are also many valuable monographs on single diseases. Valuable as books are in their place they cannot replace other publications, any more than a letter can replace a telegram. Even journals cannot keep up with the rapid developments, and parts of books are obsolete before publication.

While this discussion is limited to publications in English, it may be noted that the Journal of the American Medical Association has for several years published a bi-weekly edition of selected articles in Spanish, which, of course, is the prevailing language in Central America. It may also be said that the American Journal of Tropical Medicine has, since its origin in 1921, published summaries in Spanish after each article. Just how much value this practice has been, cannot be stated, but it is an attempt to increase the usefulness of the Journal by recognizing the great importance of Spanish civilization in the Tropics of the Americas.

It will be noted that a number of these publications have the support of institutions, and this is very necessary in these days of increased cost of illustration, tabulation and publication in journals. Several of these journals, however, are simply struggling individual journals. If you will allow a personal remark, it is a matter of record that the Secretary-Treasurer of The American Society of Tropical Medicine, and the Editor of the "Journal" each receive $25.00 a year for their labors. It is encouraging to note that philanthropic support of medicine is beginning to include publications as well as buildings.

After all, the individual is the conscious unit, and while mass effort and equipment are justly emphasized, the battles of science are fought and won, or lost, by the struggling personality. The individual worker should be encouraged by prompt and adequate publication. On the other hand, the editor must see that the urge of the *ego* does not interfere with the social aim to be achieved by the work.

In short, my argument is for increasing recognition of, and organization in, publication in tropical medicine. Along with expenses for buildings, laboratories, physicians and workers, the budget should provide for means of record and transmission. Folklore methods have no place in science. When a new institution or school is founded, means of publication should be carefully considered. If the budget is sufficient for a permanent series of bulletins, these should be provided for. Otherwise, existing agencies should be used.

In the swirl of modern life an emphasis on ideals and standards is more than ever needed. Medicine has too

great a mission to allow itself to drift, in the matter of records. There should be regular ways of record from the first flicker of an idea in the brain of the worker, through the society or journal, to the abstract journal and the world at large.

The author of "The Grand Strategy of Evolution," in a striking passage on humanity as an organism, the new social Leviathan, says:

> The Universe is its habitat, the earth its den, and the earth like an egg, is a well-provisioned residence. In the narrow cleft, between the more substantial earth and the blanket of its enveloping atmosphere, it lives and moves and multiplies; riding free the currents of terrestrial circulation; creeping into inviting valleys; crossing nature's bridges as they emerge; and following up the favoring shores of ancient causeways; spreading out where life is easier in denser racial spots and larger sprawling patches; linked over No-Man's Land by thread-like filaments of interlacing traffic; or intermingling hostile bloods, and merging spots and patches into one,— the living film at last grows around the world, shutting in its cosmic heritage. East then meets west, and north meets south, on common territory.
>
> Even so, in a growing embryo, the network of initial blastodermic cells spreads from its initial point over all the surface of its provisioning sphere, inclosing within itself its parental heritage.

As this process goes on, and man becomes more conscious of his destiny and more able to control it, how necessary it is that consciousness applied to physical and mental ills of the vast tropical zone shall have sufficient means of record. How urgent is the need for the encouragement of the individual worker in the hot countries, by adequate publication of worthy efforts! Such are the motives which should animate our editors in their particular labors.

DISCUSSION

Dr. George H. Simmons (Opening the Discussion).— The American Journal of Tropical Medicine is merely one form of scientific publication devoted to a specialty (in this case, diseases of the Tropics) such as The American Journal of Anatomy, The Journal of Infectious Diseases, and The American Journal of Physiology. The same problem is connected with all such publications: They appeal to a small group and, consequently, the circulation is small. These journals must be prepared to publish illustrations,

which require good paper and good printing, and connected with which there is considerable expense. It is the problem of supplying a high-class journal at a nominal figure. And it is made more difficult for the simple reason that nearly all of those especially interested in this class of publication are the younger men of moderate income.

It would, of course, be ideal if the United States Government would liberally support the journal edited by Major Nichols; yet this is too ideal to be expected. The American Medical Association is trying to meet the proposition, so far as concerns journals devoted to special practice of medicine. It is now publishing 5 such journals, practically at cost. It is possible to make the price low because the Association has its own plant and staff, and because paper is bought in large quantities and, therefore, at a low price. As Major Nichols has said, we publish a Spanish Edition of "The Journal," taking the best out of the English Edition and putting it into the Spanish. The Spanish Edition however, is published at a loss, one-half of which is borne by the Rockefeller Foundation.

I do not see why the Association would not be justified in fathering "The American Journal of Tropical Medicine." What is needed is a good journal, published at a fair price, and made accessible to all the men interested and working in tropical diseases.

I should like to emphasize what Major Nichols has mentioned, viz.: that authors should print summaries or conclusions, or both. If this were done, such articles would be abstracted in practically every journal that claims to abstract, for the simple reason that there is nothing to do but pick up the summary or conclusions. This is a matter of prime importance to authors who want their papers abstracted.

Following these remarks, Dr. Simmons then called attention to the fact that "The Journal of the American Medical Association," on request, has been supplying references to literature on any subject, but that this was satisfactory only when a good medical library was within reach of the physician asking for the data; and that "The Journal" is now supplying the literature itself, through the package system. These packages are made up of reprints, original journals, or photostatic copies of the articles. The method appeals strongly as a way of furnishing data from original sources to men who are eager to keep up with modern medicine.

Dr. Friedrich Fülleborn.— The suggestions given by Dr. Nichols and Dr. Simmons are indeed very valuable in facilitating the study of literature of tropical medicine, which is increasing year by year.

Indeed, a great many medical papers could be written in a few lines instead of some pages, if the authors would wisely restrict themselves to their personal experiences, giving the reference literature only so far as it is indispensable.

The shorter the paper is, the better it is, not only for the reader but also for the author, because only a few people can spend sufficient time on long ones; a short summary of the results should never be omitted, as pointed out by Dr. Simmons.

In following the progress of tropical medicine the splendid references and reviews of the "Tropical Disease Bulletin," of London, are a great help, and every student must be very thankful to those who sacrifice a good deal of valuable time making references, not only to the interesting papers, but to the bad and uninteresting ones also.

It is regrettable that a good deal of valuable medical literature of Spanish America is not yet reported in the reviews, and therefore is practically lost, because not all of the periodicals are sent to the reporting papers.

In no other country have I seen such a splendid and systematic organization of medical library work as in the United States, permitting one to compose such an extensive work as "The Index Catalogue of Medical and Veterinary Zoology," written by Drs. W. Stiles and S. Hassall, Washington.

Dr. Aldo Castellani.— I agree with Major Nichols that it is not much use making a new observation, and then not publishing it. At the same time, I am inclined to agree with Professor Fülleborn, that most of us write perhaps a little too much and write too lengthy articles; the greatest discovery can be described in a few lines.

I was pleased to hear Dr. Simmons — as he, and the editor of "The British Medical Journal," and the editor of "The Lancet," form the most famous editorial trio in the world — emphasize the point that every paper should have a short résumé at the end. It seems a very small point, but it is an extremely important one, as many valuable papers are now overlooked and are not abstracted because a résumé is lacking.

Major Nichols has very kindly paid a great compliment to "The Journal of Tropical Medicine," of London, of which I share the editorship with Sir James Cantlie. I should like to return the compliment. I think "The American Journal of Tropical Medicine" is beautifully gotten up and publishes exceedingly good papers, and I have no doubt that it will soon become indispensable to every worker in the Tropics.

Dr. Seale Harris.— Dr. Simmons' reference to the fact that formerly every medical college had its individual journal, reminds

me of how I happened to break into medical journalism. I was in the Medical School of the University of Alabama, at Mobile, when the editor of the medical journal, with a circulation largely among the alumni of the institution, had to give up his work, and the faculty wished the editorship onto me.

I didn't go into the proposition very carefully, but soon found that I had on my hands a journal that was losing money. It had been kept up on the income from advertisements of the class that we could not afford to continue. We immediately adopted the standard of "The Journal of the American Medical Association," and quickly found that we had one of two choices — either to broaden the scope of the journal, or have it go out of existence.

There were two other southern journals following American Medical Association standards, and both of them were losing money. We consolidated all of these 3 journals into "The Southern Medical Journal." I think that what had more to do with making a success of the Southern Medical Association and "The Southern Medical Journal" than any other one thing, was the policy of stressing articles on tropical medicine. These were needed in the South, and a journal containing a great many articles on the tropical diseases that prevailed there appealed to the physicians of the South.

We got in touch with Dr. Carter, Dr. Deeks, Dr. James, Tulane men, and all other medical schools in the South, and we established a department of tropical diseases and preventive medicine that I think has done a great deal of good. The circulation of "The Southern Medical Journal" is now (I am no longer connected with it) more than 8,000, and its readers are men really interested in medicine. The articles published are not over the heads of the general practitioners or the public-health workers who are handling tropical diseases, and preventive medicine at the same time.

"The American Journal of Tropical Medicine" has a great field; it is doing splendid work, and should publish the technical articles on tropical diseases. But a great problem in medical journalism is to get technical articles in such shape that the general practitioner who is handling these diseases, and the men working in public health and preventive medicine, can understand them, apply what is known, and get the benefit of the work done by research men in the Tropics.

If the men in research would supply non-technical articles or abstracts of those articles for publication in general journals, such as "The Journal of the American Medical Association" and "The Journal of the Southern Medical Association," this method would be of great use in getting their theories applied in the cure and prevention of tropical diseases. I believe that the Spanish

Edition of "The Journal of the American Medical Association" is going to do a great deal of good in getting to the physicians of Central and South America the essential facts regarding the treatment and prevention of tropical diseases with which the general practitioners in those countries have to deal.

Major Henry J. Nichols (*Closing the Discussion of His Own Paper*).— I should like to thank the members of the Conference who have taken part in the discussion. When I was first invited to come down here, I sent to Dr. Deeks the subject of a technical article on the work we have been doing, experimental work, in yaws; but afterward, I thought this subject should be brought up, and asked Dr. Deeks to change the title of my paper. I think the discussion brought out has been worth while.

It is very encouraging to hear Dr. Simmons say that he did not see any reason why a Journal of Tropical Medicine should not be issued under the support of the American Medical Association, and if we get into any serious difficulties later on I should like to remind Dr. Simmons of that.

I am also interested to hear Dr. Fülleborn speak of the able journals of Central America, which do not come to the attention of a great many of us. I think we should have a better system of abstracting these journals, in order that we might all benefit from the work done by the scientific men in those countries.

I wish to thank Dr. Castellani for his kind words, and hope that we shall deserve them later on.

I agree with Dr. Harris that we should have more general articles published on tropical medicine; I think we need a series of journals — special journals, general journals, and abstract journals; the more you have, of course, the more satisfactory it will be.

In Jamaica I have heard some of the workers say that they have been unable to have their papers published; they send them into the various home offices and that is the end of them.

THE GORGAS MEMORIAL INSTITUTE OF TROPICAL MEDICINE

Ernesto Zubieta, M.D.

We have listened with profound interest to the scientific contributions that have been read to the Congress, during its session, by other delegates from my country. I am particularly gratified that they have presented these numbers, since I desire to emphasize at this point that my paper lays no claim to scientific value or to original research, but is presented solely with the object of bringing to your attention the foundation, and actual progress to date, of a project which, when completed, will presage the advent of a Sanitary Era of "Health to All People in All Lands."

By your presence here you have demonstrated that the medical professions of your countries are vitally interested in the progress of that wave of health conservation which, during the last half century, has been spreading like an avalanche throughout the entire world. Therefore you will be interested in the Gorgas Memorial Institute of Tropical and Preventive Medicine that is being established in Panama in commemoration of the history-molding achievements of Major-General William Crawford Gorgas, who by his genius transformed my country, as well as several others, from a veritable hot bed of fever, disease and death into that paradise of health which it is today.

A Southerner, born in Mobile, Alabama, on October 3rd, 1854, Dr. Gorgas passed away in London on Independence Day, 1920, after 66 years of a life replete with service to mankind. To the very end he was filled with that relentless spirit of warfare against man's greatest Tropical foe, since at the time of his death he was en route to West Africa directing a commission whose object was to "write the last chapter" in the eradication of Yellow Fever. He did not finish, but his apostles of the future, in the Memorial Institute, will carry on his unfinished work until it shall have reached the objective that was his goal.

As a Medical Officer of the United States Army, it was the privilege of Dr. Gorgas to occupy the position of Health Officer of Havana, Cuba, during those stirring days when Walter Reed, Carlos Finley, Juan Guiteras and Aristides Agramonte were carrying on their remarkable experiments regarding the transmission of Yellow Fever.

Promptly accepting the theory that the Stegomyia mosquito was the sole cause of the transmission of this disease — by biting a Yellow-Fever victim not later than the 3rd day of the onset of his disease and then in turn inoculating a non-immune after 12 days — he built up a direct simple plan of action which enabled him successfully to take advantage of this discovery. This plan in 6 months eradicated Yellow Fever from Havana, where it had been endemic for 150 years, and where the death rate therefrom had been approximately 745 per annum, during the 50 years prior to 1889.

When the United States Government began the construction of the Panama Canal in 1904 it was very natural, in view of his marked success in Havana, that Dr. Gorgas should be selected to become the Chief Sanitary Officer of this new undertaking. The magnitude of the problem confronting him, upon his arrival on the Isthmus, may well be realized when it is recalled that at the time the French undertook the construction of a Canal, in 1880, Panama was considered to be the most terrible plague spot in the World. In the course of 9 years of construction activities under the French regime, 22,189 laborers died of disease — mainly Yellow Fever, Malaria and Dysentery. The official death rate of the French company, which was given as 65 per 1,000 per annum, failed to include many of the deaths occurring on the line of the Canal, and one competent observer estimates that the actual losses during the construction under their control more nearly approximated 250 lives per 1,000 employees during each year.

This, very briefly, was the situation which General Gorgas found upon his arrival in Panama. It was his responsibility and task to convert this pesthole into a healthy region; to reduce the death rate from disease, from the appalling ratio obtaining under the French regime, to that prevailing in communities in other countries subject to modern sanitation: to so reduce the morbidity rates from disease as to

assure efficiency and expedition in construction work; and to initiate such general measures as would permit the families of employees and the citizens of the country to reside there in comfort, and without detriment to their health. Those of you who were in Panama previous to 1906, and who have been there since, will agree with me that the change brought about in that place in so short a time is little short of marvelous, and nothing can compare with it in the history of preventive medicine.

The completely successful manner in which he accomplished all these apparently impossible things is now a matter of history. A few cases of Yellow Fever occurred in 1904, and a rather sharp epidemic in 1905, while in May, 1906, the last case (about which there is actually some doubt) appeared in Colon.

In 1906, the Hospital admission rate for Malaria was 821 per 1,000 per annum, while in June of 1924, the number had been reduced to 12 cases, thus showing that this ancient foe to humanity has been practically eliminated in Panama. To the efforts of Dr. Gorgas more than to any other agency, the success of the Panama Canal must be accredited. His reputation has gone forth to all the world and he is loved and revered in every household. Perhaps no other single man has accomplished so much for the well-being of humanity as did General Gorgas.

In 1916 he visited Central and South America under the auspices of the International Health Board and recommended systematic plans to eliminate Yellow Fever in well-known endemic centers, such as Guayaquil, Yucatan and in Brazil. He also advised investigation of suspected foci in Venezuela and on the West Coast of Africa. On his recommendation, a campaign was begun in Guayaquil in November, 1918, with the result that since June, 1919, that city has been free from the disease. In the meantime, General Gorgas organized Yellow Fever commissions in the other principal countries concerned. Epidemics were controlled in various parts of Central America and a serious outbreak in Peru was promptly checked. In the words of Dr. Vincent, "It is too early to predict a complete victory, but the successors of General Gorgas share his faith that within a few years time, it will be won."

Inasmuch as General Gorgas was in a large measure responsible for the marvelous improvement in health conditions that made possible the construction of the Panama Canal and which now exist in Panama, it appeared that there could be no more appropriate location selected by his many friends and admirers for a permanent memorial, which he so richly deserves, than in that city where his labors commenced in 1904 and continued until 1910. In ages past, men memorialized their heroes in bronze and stone, with the result that the monuments of the world are largely retrospective, representing some zenith of past achievement, but manifesting no vital force of inspiration except as they are interpreted by the sculptor. Such a memorial is not fitting, particularly when a world-wide humanitarian achievement has been accomplished by the unusual skill of a man.

For such a figure, the most enduring memorial is the provision of the means by which to perpetuate and continue his life work. This applies to the work of General Gorgas since he may be considered the personification of the public health era; and as an honor to this great scientist it has seemed clearly indicated for the Republic of Panama to put into execution the plan for a permanent living memorial that throughout the future will do honor in a fitting manner to this "physician to the world." To bring about this plan the Government of Panama decided in 1920 to promulgate a movement for the establishment of the Gorgas Memorial Institute of Tropical and Preventive Medicine. It announced its willingness to donate a site for the proposed memorial; to construct and equip a magnificent building which will be its permanent home; and to offer to the Institute all of the facilities that will develop from its intimate association with the New Santo Tomas Hospital which will be shortly completed in Panama, adjacent to the site of the Institute.

It is considered by every one that Panama is an ideal location for an Institute of this kind. Its geographical location and the permanent flow of traffic from all parts of the world through the Canal, make it a center or crossroad that will always furnish an unlimited amount of material for the purpose of investigation and research, while the

actual sanitary work accomplished and maintained in Panama affords an unsurpassed demonstration of the results and benefits of public-health work that can constantly be shown as a practical example to future students in the School of Tropical Medicine. The time for beginning an Institute of this sort is most appropriate, also, since it will be constructed and operated in connection with the new $3,000,000 hospital (New Santo Tomas Hospital) that the Government of Panama is completing at the present. By its intimate association with the Santo Tomas Hospital, the Gorgas Memorial Institute will derive many benefits and privileges that are absolutely essential to the successful functioning of a research and teaching institution such as it will ultimately be. On the whole, the occasion, location and time seem to be so perfectly ideal that nothing but the most complete success can be predicted for the new Institute.

Among the diseases which suggest themselves as possible for study in the Institute are malaria, yellow fever, plague, dengue, human trypanosomiasis, beri-beri, pellagra, leprosy, the various helminthic infections, cholera, the various mycoses, the myiases, etc. In addition to these, are the many unknown and undiscovered banes of existence which remain to be found out and to be made innocuous.

In order to properly functionate in the future, it is very necessary that the Gorgas Memorial Institute have available a large amount of money, and since the building site, together with the edifice and all equipment, is being donated by the Government of Panama, it has been decided by the Board of Directors to arrange to secure sufficient funds to provide a permanent endowment for it, from subscriptions and donations collected in the United States and South and Central America. Since the Institute has been incorporated in the United States and Panama, it is possible for the solicitation of funds to be commenced, and this has already been done, with very gratifiying results. The arrangements for arousing interest and securing contributions for the memorial endowment fund are in the hands of a committee headed by Doctor Franklin Martin and composed of such leading physicians and prominent citizens as Dr. Frank Billings, Dr. Ray Lyman Wilbur, Dr. William J. Mayo, Dr. George de Schweinitz, Gen. Charles D. Dawes, Mr.

Bernard Baruch, Hon. Ricardo J. Alfaro, and many other men of great prominence, who will have full and complete charge of raising the $6,000,000 that is the goal set as the amount necessary for endowing the Institute in perpetuity. The campaign is now being actively carried on, and by the end of this year it is expected that it will have been successfully concluded.

The functions of the Institute are expected to be threefold in nature. First, and probably most important, it will be a research laboratory, where under specialists and scientists of renown, the multiple obscure features regarding the causes and effects of various vague diseases will be studied. Undoubtedly the last half-century must be considered the golden age of medical progress, not only because of the immense number of new facts discovered, but also because of their practical application. Many subjects previously shrouded in what seemed to be impenetrable mystery, have yielded up their secrets. Diseases of which malaria and yellow fever are striking examples, and which have been wide-spread scourges, are now largely eradicated; surgical operations that were definitely considered to be unjustifiable and dangerous, are now performed successfully daily in the great hospitals all over the world; parts of the body that were considered superfluous, or as vestiges of some former age, are now known to be of vital importance, the net result being the relief and prevention of much suffering, the conferring of immunity and safety from certain diseases, and an increase in the expectation of life, by several years. Much has been accomplished in the past, but there remains even yet more to be done, and to carry out the chief purpose of medicine — "to keep the people well" — will be the primary and ultimate object of the investigations that are to be performed in the Gorgas Memorial Institute.

Secondly — in addition to the functions mentioned, it is intended that the Institute shall receive for post-graduate study a certain number of advanced students from various countries of the world that have problems in disease-prevention which require investigation and deserve improvement. It is to be remembered that the dangers of tropical diseases are not confined to the Tropics alone, but on account of world intercourse they are being constantly carried to

the non-tropical countries, endangering their health and well-being. A corps of men especially skilled in tropical and preventive medicine is expected to exert from this Institute an influence in teaching the control of diseases in a manner that is not surpassed in any existing institution of this nature. The new Santo Tomas Hospital, which is the equal of any in the world, will furnish an opportunity for the care, isolation, treatment and study of all patients that may be necessary as clinical material. It is expected that research workers from many countries will take advantage of the privileges offered by the Institute and that scholarships will be developed in the great educational institutions which will enable ambitious young physicians of higher attainments to acquire through the Gorgas Memorial Institute a thorough grounding in the science of disease-prevention that means so much to the well-being and happiness of all people.

The third, but by no means the least important of the functions of the Gorgas Memorial Institute will be the preparation and intelligent distribution of scientific literature to investigators and research workers throughout Latin-American and other countries of the world. Obviously, international coöperation in building a medical science depends upon communication of ideas from physician to physician, and from country to country. In the past, Hippocrates and Galen produced a vast amount of medical literature. Arabian authors transmitted it to Western Europe. Today, all countries are producing a copious literature in the various departments of modern scientific research. To the prompt interchange of information which this printed matter makes possible, is in part due the rapid progress in medical research work of the present, and the Institute will endeavor to make this feature of special value to the world.

Before concluding, I desire to bring to the attention of the Congress the inauguration of the New Santo Tomas Hospital that has been mentioned several times in this paper. This institution has been under construction for the past five years and when completed during the next few months will represent the last word in modern hospital construction and arrangement. Built in one of the most

attractive suburbs of the city of Panama, facing the Pacific Ocean, and having a normal capacity of 750 beds for patients, it is unquestionably the finest institution of the sort in South or Central America, and in the name of the Government of Panama I take this opportunity of extending a cordial invitation to all those present at this conference, to attend the inauguration ceremony of our New Hospital, which will take place on September 1, 1924.

This, in brief, gentlemen, sets forth the origin, the progress to the present, and the proposed future of the Gorgas Memorial Institute of Tropical and Preventive Medicine. To stimulate active research work; to aid in the diffusion of knowledge; to multiply personal contact among scientists; to encourage coöperation in medical education and in national public health, — all will be the means by which this Institute will seek to prove itself in every way a true memorial to that grand physician, Dr. Gorgas, whose life was filled with the spirit of promoting, not the exclusive prosperity of any one nation, but the well-being of mankind throughout the universe.

DISCUSSION

Dr. Aldo Castellani (Opening the Discussion). — I should like to say that I am in complete agreement with all that we have heard from Dr. Zubieta and Dr. Salisbury, but I should like to add a few words.

Twenty-five years ago, Ronald Ross made the discovery that malaria is carried by mosquitoes, and in this way he rendered possible Gorgas' great work. Thus we owe a great deal to Ronald Ross; his discovery has truly been of untold benefit to the human race; and millions of lives have been saved as a result of it. In London a few months ago a strong committee was formed — two ex-viceroys of India being on it — with the object of commemorating the twenty-fifth anniversary of this great discovery by founding a research institute which will bear Ross's name, and the director of which will be Ross himself.

The Ronald Ross Institute will not be a school and therefore there will be no competition with the London School or the Liverpool School, or any other school. Only research work will be carried on in the Institute, — no teaching. I may add that one of the three original founders of the London School of Tropical Medicine, Sir William Simpson, is on the Executive Committee

of the Ross Institute, and although my name has no importance whatever, I may also state that I have the honor of being on the staff of the London School of Tropical Medicine, and I have agreed to do my best for the Ross Institute because I feel sure that the work of the Ross Institute will not interfere in any way with the work of the London School.

In conclusion, I should like to make a suggestion, and this is that both the memory of the great American Gorgas, and the name of Ronald Ross, who is fortunately still with us, should be honored by this Conference by our passing a resolution to the effect that the Conference is in favor of the two institutions being founded.

Col. Bailey K. Ashford. — I desire to go on record as favoring the Gorgas Memorial as a center for scientific investigation. — Harvard has its School of Tropical Medicine, so has Tulane, and so has the University of Pennsylvania, in their respective university centers. But Columbia University has elected to place its School of Tropical Medicine in the Tropics, allying itself with the Government of Porto Rico in founding this school. It is my belief that it will be well for the Gorgas Memorial to have outposts of this kind to which it can look for coöperation, and which in turn will be benefited by the Gorgas Memorial.

Dr. H. J. Nichols.— It is fortunate that Dr. Zubieta has brought this subject before the Conference, because the Gorgas Memorial Institute should be one of the agencies to carry out many of the projects and problems raised in this Conference. To me one of the strong points about General Gorgas was his courage and independence in insisting that sanitation is primarily economic and should be based on taxation. In following this idea he thought that the single-tax method of many years ago was the proper method whereby to raise taxes, and he supported this plan in the face of opposition from strong interests.

One of the lessons of this Conference has been the importance of disease among children. This subject has been emphasized by Dr. Connor in regard to dysentery, by several speakers in regard to malaria, by Sir Leonard Rogers in regard to leprosy, and the pictures shown by Dr. Mühlens showed what terrible handicap disease can be among children. The subject also has a theoretical interest as bearing upon immunity later in life among survivors. It would be in accord with General Gorgas's broad humanitarianism if some of the work of the proposed Institute were devoted to this same subject.

THE WORK OF THE MEDICAL DEPARTMENT, UNITED STATES ARMY, IN THE TROPICS

GEORGE C. DUNHAM, M.D.

The Medical Department of the United States Army as an organization was brought into direct contact with tropical diseases in the Tropics for the first time in 1898, except for a short period during the war with Mexico, 1846-48. It was in 1898 that the United States and Spain engaged in a war which necessitated sending American troops to Cuba and to the Philippine Islands.

Prior to 1898 the United States did not maintain troops in any strictly tropical country, but during the 19th century epidemics of cholera and yellow fever appeared from time to time in various parts of the United States. Malaria was, and is still, endemic, in the United States. While these conditions brought the medical officers of the Army into contact with tropical disease, it was not until the advent of the Spanish-American War in 1898 that the Army as an organization entered the Tropics.

The United States Army now has a total strength of 134,808 officers and men. Of these 32,297 are stationed in tropical and sub-tropical regions, 7,824 in the Panama Canal Zone, 11,708 in the Philippine Islands, 11,466 in Hawaii, and 1,301 in Porto Rico. In addition to this number, there are 34,025 stationed in the southern part of the United States, which although not having a tropical climate does present certain medical problems pertaining to tropical diseases.

During and after the war with Spain, the Medical Department of the Army was called upon not only to protect the soldiers from the ravages of diseases prevalent in, or peculiar to, the Tropics, but also to protect the civilian population of the occupied territory.

In Porto Rico a situation was encountered, the solution of which was in later years to mean so much in terms of health and prosperity to the southern portions of the United States.

The medical officers of the Army found the civilian population afflicted with a condition designated at that time, for the lack of a better term, as tropical anemia. Col. Bailey K. Ashford demonstrated that the etiological factor of the so-called tropical anemia was hookworm infestation, a discovery which formed the basis for the anti-hookworm campaigns which have been of such benefit to the population of our southern states.

PHILIPPINE ISLANDS

Soon after the American occupation of the Philippine Islands, it was recognized by the medical authorities that a studied effort must be made to curb the tropical disease then prevalent in that territory. Accordingly, in 1900 a board was organized for the investigation of tropical diseases in the Philippine Islands. This board, which consisted of a varying number of medical officers, continued to function until 1915, when it was discontinued and its duties were taken over by the Army laboratory in Manila, P. I. During these 15 years the studies of the board did much to control the prevalence of tropical disease in the Philippines, to the material benefit of both the civilian population and the Army personnel. It was as a member of this board that Strong made his study of bacillary dysenteries in Manila; Craig and Ashburn demonstrated that the infecting organism of dengue could be transmitted by the Stegomyia mosquito, and Vedder carried out his work on *Beri-beri* and amœbic dysentery. In addition to these specific studies other investigations were successfully prosecuted by these and other members of the board, which served to render the Tropics more habitable for the white man from the temperate zone, and to improve the health conditions of the native population.

In 1922 another organization was perfected for the study of tropical diseases in the Philippines and designated as the United States Army Medical Department Research Board. This board is now functioning in Manila. It consists of 5 officers and the requisite number of enlisted men and civilian workers.

The primary problems presented to the Medical Depart-

ment Research Board are concerned with the prevention of disease among the troops serving in the Philippines, but their work is also coördinated with that of similar civilian bodies. During the last year and a half the attention of the Medical Department Research Board has been devoted to studies of metabolism in the Tropics, the incidence of intestinal parasitic infections, and investigations into the epidemiology of dengue. A study is also being conducted concerning the incidence of tuberculosis among the native troops.

The United States Army Medical Department Research Board itself is a permanent organization, and it is hoped that it will be maintained for many years to come. It is planned that as their terms of foreign service expire the personnel will be replaced by other specially trained individuals.

CENTRAL AMERICA AND THE WEST INDIES

This conference is particularly interested in the study of the tropical diseases of Central America. Today these diseases affect the welfare of American troops in the Panama Canal Zone, in Porto Rico, and in the southern United States.

All of you are thoroughly familiar with the history of yellow fever in Cuba and Panama. In 1900 a commission, in charge of Major Walter Reed, was sent by the War Department to Havana to study yellow fever. Walter Reed and his co-workers were able to prove that yellow fever was actually carried from person to person only by the Stegomyia mosquito. Few persons not students of tropical disease realize the far-reaching effect which the work of Walter Reed had upon the economic life of the Americas. It rendered feasible the construction of the Panama Canal and has made possible the eradication of yellow fever from the Western Hemisphere.

By the application of sanitary measures, based upon a knowledge that yellow fever was mosquito-borne, Major, later Major-General, Gorgas was able to free Havana from this disease. In 1903 Gorgas was placed in charge of the

sanitary work in the Panama Canal Zone. Despite much opposition on the ground and at home, he eventually enforced the anti-mosquito measures which eliminated yellow fever and reduced the prevalence of malaria. While today the building of the Panama Canal stands unsurpassed as an engineering feat, it is nevertheless an enduring monument to the medical profession. There can be no doubt that had not the science of tropical medicine sufficed to check the prevalence of mosquito-borne diseases, the Canal would not have been finished or would have been completed only at a terrific cost in human lives.

The first contingent of American soldiers was permanently stationed in the Canal Zone in 1911. Prior to that time, while the sanitation had been in charge of officers of the Medical Department of the Army, the population was civilian, not military.

Since the American Government took over the Panama Canal in 1903, yellow fever has been eradicated, the incidence in malaria has been markedly reduced, and what was formerly one of the most unhealthy localities in the world has been converted into one in which the health conditions compare favorably with the cities of North America. The Medical Department of the Army has been able to demonstrate that under the conditions which exist in the Panama Canal Zone the incidence of disease can be reduced to a degree which renders the health situation comparable to, or even better than, that existing in the temperate zone. The results obtained show definitely that in a restricted territory within which the population is under the absolute control of the health authorities, tropical diseases can be prevented or adequately controlled if sufficient money and labor are available. In other words, in the Tropics as in the temperate zone, good health can be purchased.

MALARIA

Malaria has always been the most serious of all tropical diseases occurring among the troops in Panama. The annual malaria morbidity rate per 1,000 soldiers is shown in the following table:

Admission Rate per 1,000

Year	*Ratio*
1911	53.92
1912	120.31
1913	145.55
1914	205.20
1915	85.55
1916	66.50
1917	109.23
1918	75.67
1919	82.18
1920	55.13
1921	109.52
1922	87.04
1923	75.31

The highest incidence was reached in 1914, when 205 cases were reported for every 1,000 men. During the decade since 1914, the prevalence of malaria has fluctuated from 55 to 110 per 1,000 per year, being 75 in 1923.

In general, anti-malaria measures have consisted of sanitating the military reservations so as to reduce the number of Anopheles mosquitoes below that which would serve to propagate the disease. For this purpose the usual anti-mosquito measures, such as drainage and filling, clearing away vegetation, and the use of oil and chemical larvacides and screening have been employed.

While malaria is classed as a tropical disease, it is not confined to tropical regions. There are in the continental United States areas where the Anopheles mosquitoes are present in sufficient numbers to transmit the parasite from one person to another. In these areas malaria is endemic and, of course, the troops stationed therein are then subjected to exposure. The largest such area includes the whole of the southeastern United States, from the Ohio River to the Gulf of Mexico, and from El Paso, Texas, and Leavenworth, Kan., eastward to the Atlantic. Other areas are to be found in the New England states and in California.

In peace times the Army in the United States is stationed on relatively small posts, which can be thoroughly sanitated, and the incidence of malaria is reduced to a minimum

in this manner. In time of war, when large camps or cantonments are utilized for the mobilization of an army, sanitation with a view to controlling malaria must be far more extensive and must include civilian territory contiguous to the camp. Under such circumstances the camp itself is sanitated by military authorities, while the surrounding territory is cared for by the Public Health Service.

Among the troops stationed in the United States it has not been necessary to resort to the prophylactic use of quinine. In Panama and in the Philippines, however, it frequently becomes necessary to require that quinine in prophylactic doses be given to the soldiers, particularly when the troops leave the sanitated areas for work or maneuvers. As a rule, the prophylactic dose of quinine used is 10 grains (.6 of a gram). This is given daily during the time that the troops are exposed to the bites of infected mosquitoes, and usually for a period of a week or 10 days after their return to a sanitated area.

DENGUE

While it is necessary that the troops be protected from tropical diseases during peace, the greater problem from a military viewpoint is that of devising methods and formulating plans for the control of such diseases in time of war. Considered from a military viewpoint, disease conditions are serious in proportion to the number of non-effectives produced; or, as it may be otherwise stated, in proportion to the effect that the disease may have upon the fighting strength of the Army. Consequently, Dengue might become a disease of great importance in military life, although the death rate is practically nil and serious complications seldom occur. Dengue is prevalent in the Philippine Islands, in the southern parts of the United States, and to a lesser degree in Panama. Within the last few years, the Dengue problem in our southern states has been complicated by the rapid increase in the number of automobile travelers, many of whom make long cross-country journeys either for pleasure or on business. Many of these motorists camp along the wayside or in organized camps, where they are exposed to the bites of mosquitoes. People traveling in

this manner through a zone where the mosquitoes are infected with the Dengue organisms are bitten and carry the infection perhaps for hundreds of miles to some other locality, where they in turn infect the local mosquitoes. In this way the automobile tourist tends to become an important factor in spreading Dengue wherever the Dengue-carrying mosquito is found.

The prevalence of Dengue in the United States Army during the last decade is shown in the following table:

DENGUE — ADMISSIONS — ENLISTED MEN (INCLUDING NATIVE TROOPS), PHILIPPINE ISLANDS AND PANAMA. RATIOS PER 1,000.

Year	Philippines	Panama
1914	24.09	——
1915	94.93	3.56
1916	11.89	16.80
1917	57.42	8.18
1918	51.41	.53
1919	26.57	——
1920	132.47	.45
1921	45.86	.14
1922	45.99	——
1923	79.07	

While this disease is not of great importance during peace times, it is conceivable that it could produce great havoc among the troops in time of war. Consequently, the Medical Department of the Army is making every effort to improve the control methods now in vogue.

ANKYLOSTOMIASIS

Hookworm infestation among the military personnel does not involve prevention to any great extent, but concerns principally the detection and the cure of those infested prior to entry into the service. The fact that the soldiers all wear shoes and that human excreta is disposed of in such a manner as to prevent soil contamination, serves to prevent the acquisition of new infestations. During the World War it was necessary to examine the feces of a large number

of soldiers recruited from the southern United States, in order to search out and treat those infested with hookworm. This work is being continued, and it is now the routine practice at our southern stations to make hookworm surveys, particularly of recruits, and to treat thoroughly all those found to have the ova in their feces. In general, carbon tetrachloride is used as the therapeutic agent in the treatment of hookworm infestation.

General

The members of the Army remain in the Tropics for only comparatively short periods of time. The term of service in Panama is 3 years, and in the Philippine Islands it is 2 years. Medical officers serving in the Tropics have given much thought to the effect which a tropical climate *per se* may have upon physical and mental efficiency, particularly in the case of Army officers. The medical authorities of the Army, as a rule, do not consider that service in the Tropics has any detrimental effect upon the efficiency of a healthy individual.

From time to time officers apply for an extension of their tours of duty in the Tropics. In such cases, where not contraindicated by an abnormal physical condition, it is the practice of the Surgeon General's Office to recommend that they be permitted to remain on tropical service for an additional period of time. The wisdom of this policy has been questioned by some of our military authorities, who believe that the tropical climate produces a deleterious effect upon the mental efficiency of the Army personnel.

The Medical Department Research Board is now endeavoring to determine whether the officers serving in the Philippine Islands are affected adversely by the tropical climate. Within the last year, other boards have been appointed in Panama and in Porto Rico to study this question. It is proposed to study the comparative mental efficiency and physical health of officers while they are in the Tropics, and prior and subsequent to such service. These investigations must extend over a number of years, but it is believed that the data obtained will be of value in determining the effect of tropic residence upon mental and physical efficiency.

OBSERVATIONS ON SOME TROPICAL DISEASES, AND MEASURES RECOMMENDED TO PREVENT THEM IN FUTURE

José Azurdia, M.D.

I.

Mr. Chairman, Ladies and Gentlemen:— Before beginning to read my contribution kindly asked for by Dr. Deeks, I have two duties to perform. The first one is to present the compliments and thanks of the Guatemalan Government to the United Fruit Company for the invitation to attend this Conference, and in doing so I must congratulate the Medical Department of the Company for the unquestionable success attained by the Conference. It appears to me that the tropical countries, to their own credit, are trying to get rid of tropical diseases, and tropical diseases are looking for a safe shelter outside the Tropics in the North and the South of the World. The Conference has dealt with problems not merely of Tropical Medicine. We have had important communications from the most famous authorities in the Old and the New World concerning many other pathological and sanitary subjects. Whatever the results of Dr. Noguchi's important investigations in yellow fever, and Dr. Kofoid's views about *Amœbiasis*, it is a real fact that this Conference will be an historical event in the progress of Tropical Medicine, because of the many important papers and spirited discussions it has been our great fortune to listen to here.

My second duty is of primary importance. It is to convey to the Conference the cordial greetings of the President of Guatemala, and also to present his invitation to all members of this meeting, ladies and gentlemen, to visit Guatemala City. For visitors and tourists my country has a great deal of interest from many points of view. You will find there ruins of great archæological importance. These are the work of the ancient Mayas, whose obelisks and monoliths demonstrate how wonderful their civilization

must have been. You will see, also, how great is the natural wealth offered to immigrants by this land of many climates. Individuals who are healthy, energetic and ready to work are consequently sure of succeeding in their efforts. And finally, you will see the beautiful and lovely scenery of valleys, forests, mountains and towering volcanoes, no less than the lakes and rivers, which are surrounded by productive plantations of sugar cane, bananas, cocoa and coffee. Our coffee is among the very best, if not the best, in the world.

In the name of the President of Guatemala, I am able to say that you may be sure that you will be received cordially and with open arms, both by my Government and by the people. I regret very much indeed that circumstances make it impossible for me to accompany you to Guatemala, but a committee of my countrymen will be appointed by the President, will meet you at Puerto Barrios, and will aid you in any possible way to see the various points of interest for which my country is famous.

Finally, I sincerely congratulate Dr. Deeks for his tact in leading this Conference so as to obtain the magnificent success we have seen.

II.

Ladies and Gentlemen: — I shall not take long for my discussion, in spite of the importance of the subject of tropical diseases to which I shall now refer:—

I think that all peoples in the world have been reluctant to adopt the laws of sanitation. This may be due to ignorance, negligence, pessimistic views of life, or religious training. Sanitation, in its real meaning, has been founded upon and developed from the investigations and discoveries of that famous and glorious savant,— Pasteur. France has been the theoretical teacher of sanitation, but not the pioneer in practice. The United States of America has undoubtedly played a tremendous rôle in extending and intensifying sanitation, and that country has been the practical applicant of scientific discoveries. It has equipped itself fully for the work of sanitation, and has therefore succeeded in its efforts and undertakings along this direction.

Spanish America ought to follow that wise example, and endeavour to free itself from endemic and epidemic diseases throughout the Continent. Central American countries (sometimes called the Balkans of America, on account of their revolutions and internal strife) are infested with Malaria, Dysentery, *Filaria Onchocerca*, Uncinariasis, and some other intestinal worms. The populations, comprised of Indians, Negroes, Europeans, Mestizos and the offsprings of these different races intermixed in varying degrees, have been totally negligent and ignorant of all phases of sanitation. They have no such vision of Life as that firmly possessed by Europeans. They do not consider Life as the supreme gift of Nature. They do not take Life seriously, but merely as an incident. That, in my opinion, is the reason for their indifference to progress and their reluctance to assume their proper place in the forward march of civilization. That is why commerce, industry, navigation and agriculture do not improve rapidly in their midst but, on the contrary, remain stationary and dormant for years, and sometimes generations; that is why revolutions occur frequently and bloodshed results, irrespective of the dire results which are bound to ensue from such conflicts repeated at frequent intervals.

Similarly, endemic diseases are permitted to exist, and epidemic diseases develop and extend themselves, with practically no effort on the part of the Central American countries to combat and overcome them. Furthermore, it is a lamentable but true statement when we observe that the present inhabitants of these countries have retrogressed rather than progressed, as compared to the pre-Columbian Americans. The Mayas, that is to say, the racial stock which founded and developed the two primitive empires of pre-Columbian existence in Central America, were not warriors or conquerors. Judging from their monuments and bas-reliefs recently discovered, they were civilized and peace-loving people engaged principally in agricultural and mining pursuits. With these ideals, they naturally devoted considerable attention and study to the observation of Nature in its various aspects, and hence developed a deep and thorough understanding and knowledge of astrology, astronomy and meteorology, as indicated by their accurate and

really wonderful calendar. The astronomical calculations, the division of time, the prognostications of weather conditions utilized in connection with sowing and harvesting crops, as revealed even now by the natives in their traditional methods of agriculture — demonstrate clearly that their ancestors were clever and careful observers of Nature, and that they applied their wisdom in this direction minutely and wisely in connection with gaining their means of livelihood.

It is impossible to believe that a nation — the Maya Empire — could be so far advanced along other lines and remain ignorant of medicine and its branches — Hygiene and Sanitation. It is, in fact, demonstrated that in dentistry and surgery they were advanced people. They practiced trepanation of the skull, and also followed a real orthopedical method for the enlargement of the skull, although we are not familiar with the purpose of the latter operation. They were well acquainted with the medicinal properties of leaves, flowers and roots, and used them to heal and cure their diseases and maladies. While they had formal prayers, and appealed to their superstitions and gods to rid themselves of diseases, the same thing can be said of the ancient inhabitants of Egypt, Greece and Rome; but in addition they had pharmaceutical and chemical substances for the purpose of coping with such conditions. The old historical documents of pre-Columbian origin, translated by the early Spanish settlers, as well as the narratives of the Spanish conquerors, make references to some epidemic diseases which may have been small-pox, yellow fever and malaria.

The natives applied the drugs obtained from the plants, at that time; and the records available indicate that their fathers had done so before them.

It is also recorded that the women were fond of perfumes, so that they must have been familiar with the methods of extracting essences from flowers.

The Peruvians in South America employed cinchona. Was this plant unknown, and its virtues and properties unused and ignored by the Mayas? Did they not use cinchona on their plantations? Had they not also other herbs efficacious for the treatment of malaria, hookworm and yellow fever? If we bear in mind their cognizance of the ways of

nature, and the advanced state of their civilization, it is incredible that they were backward in developing measures to cope with these tropical diseases. Now, how are we to explain the loss of this knowledge, and the total absence of any conception of the methods of treatment and the cure of these diseases among the native population of the present day?

It may be logically assumed that it is the result of their legitimate hatred of the Spanish conquerors; so that, instead of acquainting those conquerors with the methods of preventing and curing these and kindred diseases prevalent among them, they were probably keen and resolute in keeping the secret of their therapeutical means for prevention and cure from the Spaniards. It may be that they conceived this means of fighting the invaders, believing that ultimately the endemic diseases would force the conquerors to withdraw — and we can readily understand their attitude toward the foreigners who came to their countries with the sole object of benefiting by injuring and robbing the natives, and who intended to subjugate the native population and settle the land, degrading the original inhabitants and establishing themselves as the ruling class. We can also quickly comprehend the attitude presumed, if we keep in mind that the Indians who had previously been free were subjected to abject slavery by their conquerors.

Times have totally changed. Wider views and brighter prospects have been opened to the nations. After the hecatomb to which all races contributed during the Great War, humanity is earnestly seeking a solution to prevent such catastrophes in future, and striving energetically toward an era of universal peace. Civilization seems to be foundering, and the shipwreck may be complete. International commerce and trade will help to save it. Commerce must be intensively increased by all men of good-will, and it is an axiomatic truth that commerce is impossible on an extensive international scale without sanitation. There will never be uninterrupted productive work, wealth and capital unless sanitation and healthy conditions are produced, and scientifically maintained, among all nations anxious to obtain comfort, prosperity, riches and peace.

There have previously been international congresses and

conferences which have accomplished a great deal towards solving health problems. Their resolutions and recommendations have been more or less adopted and executed, but not as quickly as need demands. Theory has been slowly turned into practice. The United Fruit Company has taken these views in mind, and is now the leader of sanitation and health along the Caribbean Sea, not for the Company's benefit only, but also for the improvement of trade and commerce and humanity's welfare. The United Fruit Company is the first commercial firm engaged in showing to the world the practical results of their humanitarian campaign; and it is necessary to request the hearty help and coöperation of all concerned who live on the coasts of the Caribbean Sea, to follow this beneficial example.

With the purpose of furthering such an enterprise, I propose that this Conference recommend the following resolutions:—

1st.— That it is desirable that the commercial, industrial and agricultural concerns in Central America unite for the purpose of combating the tropical diseases, a real drawback to the improvement and development of industry, agriculture and international commerce.

2nd.— That all scientific and medical institutions coöperate for the prevention and cure of malaria, uncinariasis, dysentery and yellow fever by lectures, publications and any other means likely to bring practical results.

3rd.— That for this propaganda the monetary help of all business men be obtained.

4th.— That all civil and military authorities and corporations render effective help in the maintenance of sanitary conditions in towns and villages as well as in the rural localities, in order that the work may be thoroughly done.

5th.— That the governments concerned — i.e., the United States of America, Mexico, Central American Republics, England and France (on account of their Colonies) hold recognized and regular periodical meetings and conferences, to determine practical means of contending with all problems concerning the tropical diseases common to them all. These international conferences must be held every two years in the cities or towns which may be considered most desirable.

6th.— That the National Red Cross in the countries

mentioned render all coöperation and aid in the effort to secure the total extinction of all tropical diseases in the communities under their own jurisdiction.

7th.— That there be founded in one of the Central American countries mutually agreed upon by the United States of America, Mexico, the Central American Republics (including Cuba and all islands in the Caribbean Sea), England and France (on account of their Colonies) an efficient School of Tropical Diseases and the necessary branches.

8th.— That Sanitation and Public Health are the firm and essential basis for wealth and the economic life of a people, and that it is therefore desirable that the government in Central American countries include in their political platforms a broad programme for both sanitation and public health, in order to promote the financial life of their own countries.

TICK-BITING EXPERIMENTS IN BOVINE AND CERVINE PIROPLASMOSIS

Herbert C. Clark, M.D., and James Zetek

The presence of equine piroplasmosis in Panama was first reported by Darling in 1913[1] and, although the presence of the bovine type also, was suspected at that time, it was not absolutely determined until the end of 1916[2] when the cattle industry of the Canal Zone first became an important business feature. We noted piroplasmosis of the dog, too, at this time.

A survey for the general index of the disease among both domestic and wild animals was then started, and during the month of February, 1917 (dry season), one of us had an opportunity to investigate animals in the lower part of the basin of the Chagres river. Piroplasmosis was found in the native cattle of the basin and in the white-tailed deer (*Odocoileus chiriquensis* Allen). Ten of these deer were killed, and four of them were positive for piroplasma, showing, perhaps, a "carrier state" of the disease. These parasites possessed dimensions, morphology, and staining characteristics so like those of the parasites found in cattle that we were led into some experimental efforts to see what might happen when the deer parasite was introduced into a calf and, on the other hand, what would result if the cattle parasite were introduced into young deer.

The World War interfered at this time, and our attempt was delayed until the year 1920. Then efforts were made to find suitable animals for the purpose. It was suggested to us that the scope of the work might be enlarged by using the offspring of adult female ticks removed from animals known to have the disease. One of us, by accompanying the Tabernilla Hunting Club of the Canal Zone on a large num-

[1] Darling, S. T.: "Equine Piroplasmosis," *Journ. Infect. Dis.*, 1913, 13, p. 197.

[2] Clark, H. C.: "Piroplasmosis of Cattle in Panama," *Journ. Infect. Dis.*, 1918, Vol. 22, No. 2, pp. 159–168.

[3] Bishopp, F. C.: Entomologist; "Insects Affecting the Health of Animals," *Bureau of Entomology, U. S. Dept. of Agr.*

ber of its hunts, finally succeeded in examining, immediately after their death, 42 white-tailed deer. All of them were killed within from a mile to five miles of the Canal or the Gatun Lake area, and the jungle was in more or less close proximity to some of the large Canal-zone cattle pastures. Although nearly all of these animals were in prime physical condition, the majority revealed piroplasma in some of the capillary blood cells of brain films; and in a few cases long searches would also reveal them in blood films of the peripheral circulation.

In the series, the only deer that gave evidence of serious illness not due to injury or old gunshot wounds was a half-grown white-tailed deer shot after a very short run near Gamboa, C.Z. It was killed on April 11, 1920, where the jungle bordered on a cattle pasture. This animal was extremely emaciated, and very heavily infested with ticks. The ears were so completely covered with them that we cut off the organs near the head, and took them back to the laboratory with the ticks attached, rather than attempt to remove the parasites at the spot of the kill.

The lungs of this deer revealed an extensive verminous broncho-pneumonia, and the bronchial tree contained many thread-like worms, probably of the Strongylus type. In addition, the liver was extensively involved by lesions, produced by some type of fluke. The brain films, rib-marrow, spleen, and peripheral blood in this case showed abundant piroplasma, as well as a large trypanosome believed quite similar, if not identical, to *T. theileri*. The acute piroplasmosis found perhaps represents a development that occurred following the animal's decline in health caused by the other diseases present, since, under ordinary conditions, piroplasmosis does not seem to be much of a handicap to deer.

The vast majority of the ticks removed from this deer proved to be *Margaropus annulatus australis*, the common cattle-tick, but a large number of *Amblyomma cayenense* were also present.

SOURCE OF TICK MATERIAL FOR THE EXPERIMENTS

The progeny of the adult female ticks (*Margaropus annulatus australis*) taken from this sick deer were used in the biting experiment performed on a non-immune calf from the

Corozal Dairy. This calf was the offspring of an imported Jersey bull and a native cow.

No work was done with the adult female *Amblyomma cayenense* ticks because not enough satisfactory animals were available.

The ticks used in the biting experiments on the deer were obtained from the Panama City slaughter house. We removed adult female *Margaropus annulatus australis* and *Amblyomma cayenense* from nine steers as soon as the animals were killed, and then we took crushed tissue-films from the cortex of the brain of each steer. This last step was taken to determine approximately which steers were the worst "carriers" of the parasite (*Babesia bigeminum*). The cattle ticks (*Margaropus annulatus australis*) were selected from the three steers that showed the greatest number of parasites in the brain films.

TICK TECHNIQUE

We wanted to secure an abundance of tick offspring, so all the adult females were placed in a deep moistening-jar upon clean, fine, slightly moist sand. As the adult females are gregarious in habits, the eggs were laid in a few big bunches, easily lifted up with a spatula and transferred into the breeding-tubes. Eggs were laid in large quantities.

These eggs were transferred into clean glass tubes 20 cm. by 5 cm., and in the bottom of each was about 8 cm. of clean sand, slightly moistened. Owing to the excessive evaporation, it was necessary to arrange some means for keeping these tubes provided with the proper amount of moisture. Therefore, the ends of the tubes were sunk to about 10 cm. in fine sand in the jar. This sand was kept moist by means of tubes that reached to the bottom of the jar. Thus enough moisture permeated upward through the jar of sand into the egg tubes. Each egg tube was provided with a strip of gauze that reached to the top. This gauze was for the purpose of giving to the young larvae, when they emerged, something suitable upon which to climb. The tubes were securely covered with cloth, to prevent the accidental escape of larvae into our rooms and eventually into the animal rooms. The jar of egg tubes was placed in a pan of water and the rim of the pan was smeared with tanglefoot.

Calf Experiment. — Ear bags and an abdominal band were used to apply the tick larvae. Several tubes of tick larvae, containing about 3,000 individuals in all, were taken to the isolation shed; and since these larvae were nearly all gathered on the tops of the gauze strips, it was necessary only to take out these strips and place them within the ear bags and the belly band. Judging from the number of ticks that took hold of the host, this method of applying them was satisfactory.

To prevent other ticks from invading the calf shed, as well as to prevent our infected ticks from scattering into surrounding lots, a strip of grass, 1.5 meters wide, was cut all around the shed and heavily sprayed with crude oil and a larvacide mixture. The calf was removed from the laboratory to the isolation shed in a truck, and precautions were observed to prevent ticks from getting to the animal en route. Temperature records and blood films were taken daily for some time before the biting, and then continued twice a day for nearly two months afterward.

Deer Experiment. — This was performed in one of the concrete rooms of the Board of Health Laboratory. To prevent any of the ticks from getting into the neighboring animal rooms, a continuous band of lime-sulphur wash was painted around the deer room. The seed ticks were applied to the deer, again in the same manner, except that ear bags were not used. Instead, a bunch of these ticks were rubbed inside of the ear. This method was effective, as the ears were well covered with ticks. Wherever the deer's tongue could reach, the ticks were very soon removed, but fortunately some regions were safe for tick development. When adult ticks began to fall off the deer, we collected enough to almost fill a half-liter flask. This quantity represents a very heavy infestation, perhaps more than usually occurs in nature unless the animal is very weak from some injury or illness.

SUMMARY OF TICK EXPERIMENTS

Calf Experiment. — The animal was a young bull calf from an imported Jersey bull and a native cow. For about one month it was confined in the screened, concrete dairy building of the Corozal Hospital Dairy, and was kept under

close observation for a long time before the biting experiment started. The calf, believed to have been non-immune, was taken to the isolation shed for the biting experiment, May 11, 1920, and the larvae from the deer ticks (*Margaropus annulatus australis*) were applied that same afternoon and the next day.

Within two days, these seed ticks became attached. On May 28, the ticks were large and plentiful, and very annoying to the calf. On May 30 the animal had a very fetid diarrhea, and a temperature record of 104F. It was weak and dull, but always drank its pailful of water and milk. On May 31 the ticks began to fall off. Thus a period of 18 to 20 days elapsed after the seed ticks attached themselves to the host.

No special attention was given to the bionomics of the ectoparasite. The average duration of the several instars was: egg instar 22 days; larval stage 5 days; nymph stage 9 days; and the adult period until the females dropped off the host, 8 days. This means a period of about 45 days after the eggs were deposited.

Inoculations performed for immunization of non-immune imported cattle, with 2 cc. of defibrinated blood from slaughter house animals (Panama City) has always been followed by a "take"; but fewer than 10% of the animals ever show an abundance of parasites in the daily peripheral blood-examinations, which extend over a period of 2 months. It is the rule, however, to find them for the first time about the 8th, 9th or 10th day following the inoculation.

In this calf experiment, in which larval ticks were used to convey the disease, the blood films were found positive in a meager way, after the biting, on the following days: 10th, 13th, 14th, 15th, 19th, 20th, 21st, 23rd, and 24th. They were always in scant number and required from 10 to 30 minutes' search to locate them. They were more easily found on the 19th and 20th days after the biting. The calf, which never revealed a significant decrease in its hemoglobin index, and never was known to pass red urine, was returned to the dairy about two months after the biting experiment. There it thrived as well as the other calves of its age.

Deer Experiment. — We started this experiment with 2 young deer. Each was a distinct species: *Odocoileus chiri-*

quensis Allen (the common lowland white-tailed deer) and *Mazama sartorii reperticia* Goldman (the brocket deer, "cabra de monte," or highland forest deer). This brocket deer was the only one of its kind that we had a chance to examine; and although it is not considered as good a host for piroplasma as the white-tailed deer, yet circumstances forced us to use it in this instance.

The little white-tailed fawn, from which we hoped to get the more striking results, was very wild and unmanageable, and during one of its frantic efforts to escape, it broke its back and one shoulder. It was chloroformed, and an autopsy was performed. Its death occurred just four days after the biting was done. The seed ticks were found to be firmly attached to its pelt. No parasites suggestive of piroplasmosis were found in films from the organs or blood.

The brocket deer was acquired while still very young. Spotted markings were not as distinct in this type as in the white-tailed deer, but it was only a few weeks old. This specimen was the nearest approach to a non-immune deer that we could secure. It was very tame, an excellent animal from the standpoint of behavior, but the type is probably not as satisfactory a host for the piroplasma as the white-tailed animal. The seed ticks were applied July 17, 1920. About 6,000 larvae were used, and within 2 days they were attached. As soon as they began to show a marked increase in size, they caused considerable irritation. The 10th, 11th and 12th days after the biting, the deer became dull and irritable, spent most of the time lying down, and would not rush to the door when his food arrived as was usual in his case. However, he never failed to eat and drink if food and water were placed near him during these days. After the ticks fell off, he regained his former state of great activity.

The gorged ticks began to fall off on August 6, or 20 to 21 days from the time they were applied. The egg instar was about 27 days, somewhat longer than in the calf experiment. This increase is accounted for by the variations in the relative humidity during the incubation period. The deer's temperature curve, before the biting, was 101 to 102 by rectum; and the greatest rise in temperature after the biting was to 103.5 on the 9th day, and to 103 on the 25th day. A few

piroplasma were found in blood films on the 10th, 15th and 25th days after the biting; otherwise all films were negative. We never noted hemoglobinuria, but such a condition might have escaped our attention in the case of the deer. Its hemoglobin was never below 80%. At the close of the experiment (about two months after the biting) the animal was placed in a yard in Panama City, with a number of white-tailed deer, in order that it might have more range, and still be near enough to be examined at times. It died some weeks afterward, and was carried off by the Sanitary Department before we could secure an autopsy. We cannot say whether piroplasmosis had anything to do with its death. This little brocket buck was much smaller than the white-tailed buck in the yard with it, and it seems quite likely that injuries received in a fight between them may have resulted fatally.

FURTHER WORK NEEDED

In these experiments only one deer and one calf could be secured at the time the tick larvae were ready for use. It is not always possible, even in cattle, to get a striking clinical picture of this disease, with abundant parasites in the peripheral blood films. Therefore it would have been much more desirable to use at least a dozen white-tailed deer and a dozen high-bred, imported, yearling stock for the work. Suitable animals can be obtained only with great difficulty in the Tropics, where ticks are so numerous.

It is hoped that this report will interest others who may be in a better position to repeat these experiments. Any non-tick belt would furnish satisfactory cattle and deer, or the correct species could be bred and raised under tick-free conditions in zoölogical gardens. Ticks could be shipped to such a region when they were nearly ready to deposit their eggs. The ease with which the ticks can be secured, developed and applied to the host, makes the actual experimental work easy. The great difficulty is to secure absolutely suitable animals. A white-tailed deer specimen (in a zoölogical garden) that is free from other diseases, will not be seriously inconvenienced by piroplasmosis; but the cattle may be lost, as about 10% of the adult, non-immune, high-bred cattle given immunization inoculations in Panama, suffer a serious attack of the disease.

SUMMARY

1. It is certain that mature *Margaropus annulatus australis* and *Amblyoma cayenense* can both be found attached to cattle and deer, in Panama. We have made no experiments with the last-named type.

2. Hunting experience in and near the Canal Zone has afforded one of us an excellent opportunity to examine a relatively large number of white-tailed deer (*Odocoileus chiriquensis* Allen). These animals usually showed the presence of a scant number of piroplasma in some of the blood cells of the cortical capillaries of the brain (crushed brain-cortex film); and in some instances the peripheral blood film showed the parasites. One deer suffering from a verminous broncho-pneumonia and liver-fluke disease had an associated acute attack of piroplasmosis.

3. In one instance, the progeny of ticks removed from this sick deer were capable of producing a mild attack of piroplasmosis in a half-breed, non-immune calf. The ticks in question were *Margaropus annulatus australis*.

4. In another instance, a mild attack of piroplasmosis was produced in a brocket deer (*Mazama sartorii reperticia* Goldman) by having the animal bitten profusely with the progeny of *Margaropus annulatus australis*, taken from prime beef-cattle at the time these animals were slaughtered in Panama City.

5. Probably cervine and bovine piroplasma are identical. If not, then the tick *Margaropus annulatus australis* is capable of being a carrier agent for two types of piroplasma, and the tick uses the deer as well as cattle for a host.

6. The practical value of these experiments is in the indication that the deer makes an important reservoir for cattle piroplasmosis.

These experiments were conducted at the Board of Health Laboratory of The Panama Canal, while the authors were serving on that staff respectively as pathologist and entomologist.

DISCUSSION

Dr. R. W. Hegner (*Opening the Discussion*). — It seems to me that Dr. Clark need not apologize for presenting before this con-

ference a paper on an animal disease, inasmuch as a large part of what we know regarding many of the human diseases was first learned through a study of the lower forms of life. I need only mention the transmission of malaria by the mosquito and the determination of the significance of exflagellation in malaria, both of which were discovered by experiments on birds. Furthermore, a number of organisms have been reported from man as causes of diseases that are very similar in appearance to piroplasmas, and it may be that these organisms are actually etiological agents of human disease.

Dr. Clark's problem, I would say, is really one of specificity of parasite and host. The protozoa differ widely, in regard to the specificity of the host. Some of them seem to be very specific with regard to the host — as, for example, the intestinal flagellates of the genus Giardia, which inhabit the duodenum of man and are also found in a number of lower animals, like rodents, tadpoles, and certain birds. In certain other flagellates, the herpetomonads, the parasite does not seem to be specific with respect to the host. Flagellates of a single species may occur in the intestines of flies of different species or genera.

Dr. Clark did very well, considering the circumstances under which he was working. I have talked with him about the subject, and hope that we can make arrangements so that the work can be continued by coöperation between his laboratory in the Tropics and our laboratory in the North. There are probably many problems that can be worked out satisfactorily in this way.

Dr. J. G. Thomson. — I have been extremely interested in the valuable contribution of Dr. Clark. It is a remarkable fact that in Rhodesia indigenous cattle suffering from chronic piroplasmosis rarely show symptoms of red water. In South Africa, where the importation of thoroughbred cattle from England is common, the prevention of red water in these non-immune animals is a matter of great economic importance. Unless immunized, these animals are in grave danger of contracting severe piroplasmosis accompanied by the passage of red water.

It seems to me that we have in blackwater fever in man, and in red water in cattle, two very similar conditions. Indigenous cattle seldom suffer from acute symptoms with the passage of red water, and the indigenous native seldom suffers from black water. The non-immunes, however, in both instances suffer from haemoglobinuria.

Dr. Herbert C. Clark (*Closing the Discussion of His Own Paper*). — In reply to Dr. Thomson, I may say that I have examined a large number of beef animals in the Panama slaughter-house for "red

water" or "blackwater," but never found a case in these carriers of the disease. It does, however, occur in native animals if their vitality is reduced by injury, by some other disease, or by starvation. Nearly all imported non-immune cattle, if followed through the full course of the acute attack of piroplasmosis, will show a short period or two of hemoglobinuria, and about 20% of them will show a very serious drop in their hemoglobin index.

One of our quartermasters told me that the expense of proper feeding and dipping of the wild, native beef-animals, for a few months before they were killed, was more than returned by the increase in weight of the animals. I don't know what values to place on the reduction of tick infestation and on the increase in quantity of the feed in this instance.

Regarding piroplasma in the deer, I may say that the only record I could find in the literature at my disposal was in Kolle-Wassermann. The statement was made by them that piroplasma was found in some deer in a German zoölogical garden, but that it was probably a type specific for that animal.

DERRENGADERA — THE EFFECT OF "BAYER 205" ON THE TRYPANOSOMA VENEZUELENSE

Juan Iturbe, M.D.

It is now 100 years since the political chief of the upper Apure begged aid of the central Government to combat a disease which attacked horses in the llanos of Venezuela, causing enormous losses to cattle-breeders.

Rangel (1905) discovered the nature of the disease, and at the same time showed that it presented two different clinical aspects: the *Peste boba* and the *Derrengadera*.

In 1916 on a scientific excursion with González to a ranch called "Jabillal," situated near Cagua, we succeeded in transmitting the disease to laboratory animals by injecting the intestinal contents of a kind of gad-fly, which is thought to be the species *Tabanus importunus* Wied., (*Howard and Knab of Washington*). Tejera and Leger (1920) have thrown new light on the study of the biology of the trypanosome which causes the disease.

In the infected parts of our llanos, horse Trypanosomiasis presents the two different clinical aspects mentioned above:

Peste Boba

The disease begins with fever of 40° to 41°; the diseased horse loses its vivacity and its skin becomes dry and harsh. These symptoms are always accompanied by inflammations of the conjunctiva, with lachrymation. After suffering this initial attack, the animal seems to recover its health, and the only symptoms still remaining are a hesitating and uncertain gait, a roughness of the hair, and, above all, patches of alopecia scattered over its skin. The nasal and buccal mucosæ show a profound state of anemia, and it is not unusual to observe iritis and hæmorrhage in the interior chamber of the eye. To this description may be added a tachycardia accompanied by so rapid a respiration that it sometimes merges into fits of dyspnoea. The urine passed in small quantities contains albumin, and in some cases anuria is observed.

During this phase of the Trypanosomiasis, edema of the eye-lids, face (hermosura), chest and hams of the horse, is commonly observed. On the abdomen, the aspect of the swelling is circular, with an ample ring around its edge. (Peste de budare.)

After a period which lasts from 15 to 60 days, the disease terminates fatally in 80% of the cases.

DERRENGADERA

This second clinical modification of equine Trypanosomiasis of the llanos of Venezuela, kills hundreds of horses annually. It is also found spontaneously in certain types of the fauna peculiar to those regions. Indeed, its presence can frequently be detected also in mules and asses, in dogs, chigüires (Hydrochœrus capivara), foxes (Canis azaræ), and in large monkeys called araguatos (Micetes ursinus).

Derrengadera, besides presenting the symptoms peculiar to the *Peste boba*, is characterized by the rapidity with which difficulties of movement appear: symmetrical or asymmetrical paresis, and, though of rare occurrence, even complete paralysis of the hind-quarters. At first the horse can walk well, with an almost imperceptible halting. Then it is unable to bend its leg upon the thigh, whereupon it drags the end of its hoof, so that its foot-marks are scarcely visible. It cannot maintain its equilibrium when standing, being forced to spread out its hind-legs so as to increase its base of sustentation. When it walks, a rigid state of the legs is noticeable, and the muscles do not respond to the central excitation. These grave symptoms notwithstanding, it can run if necessary. As the sickness progresses, the paralytic phenomena become more pronounced. When the horse walks, it describes semicircles to the right and to the left, and when it falls to the ground it tries in vain to rise. At last, on the point of death, it suffers convulsions and its respiration is stertorous. This paralytic form of the Trypanosomiasis of the llanos of Venezuela has a mortality of 100%.

Rangel (1905) laid down that the two kinds of disease have as a common etiological agent a trypanosome measuring from 18 to 20 micra by 1.17 micra.

Mesnil (1910) proved that this protozoön is altogether

different from the *Trypanosoma equinum* in regard to its morphology; it resembles the *Trypanosoma evansi*, but is a completely different species: *Trypanosoma venezuelense*.

Although Venezuelan Trypanosomiasis is very much like the *mal de caderas* of the Argentine Republic, it differs clinically from it through the absence of hæmoglobinuria. Moreover, from a morphological point of view, it is impossible to confuse the two specific agents. And lastly, in its virulence and also in the duration of the sickness caused by the disease, *Trypanosoma venezuelense* differs from the *Trypanosoma equinum* and from the *mal de caderas*.

Leger and Tejera (1920) have proved that the *Trypanosoma venezuelense* and the *Trypanosoma evansi* are two distinct species, as is shown by their different pathogenic action on animals, by their different resistance to chemotherapeutical agents, and lastly by the immunity reagents.

EXPERIMENTS

The virus we employed in our investigations was gathered towards the end of 1915 from horses infected in the llanos and brought to Cagua. From that time to this, we have succeeded in getting a trypanosome with fixed virulence, by successive infections of laboratory animals.

Guinea-Pig.— With an intraperitoneal infection, our virus produces the death of the animal within 15 or 25 days. The trypanosomes increase daily in the peripheral circulation, as may be seen in the film projection which is to follow this exposition; and contrary to the assertions of some investigators, they are seen in great numbers a few hours before the death of the animal. The autopsy of the animal reveals generalized edema and hæmorrhage of all the organs.

Gray Mouse.—As a general rule, 3 days after the subcutaneous injection, trypanosomes are found in the blood, and death supervenes in 2 weeks.

Horse.—The 14th of November, 1916, we inoculated a horse, 5 years old, with 3 c.c. of blood taken from a guinea-pig. The 18th of November it had trypanosomes in its blood; the 27th of the same month we could count 10 per field of vision.

The temperature was 40°, and the progressive emaciation of the animal was accompanied by conjunctivitis, oliguria and slight swellings in the hams; 45 days following the

inoculation, that is, on the 3rd of January, 1917, the horse fell sideways to the ground and died during convulsions.

INTERMEDIATE HOST

In the year 1916, González and I succeeded in obtaining the transmission of the disease to laboratory animals, by means of injections composed of the intestinal contents of specimens of tabani which had stung infected horses. These insects were classified by Howard and Knab of the Entomological Bureau of Washington as *Tabanus importunus Wied.* Subsequent experiments will clear up the part played by this diptera as a transmitting agent of Derrengadera.

TREATMENT

The good results obtained by Van Saceghem (1915) with the administration of emetic to horned cattle affected with *Trypanosoma cazalboui*, induced us to try the effect of acid monotartrate of antimony and potassium in cases of Derrengadera. Intramuscular and intravenous injections of emetic in doses of 4 to 5 milligrams to the kilogram, cause the *Trypanosoma venezuelense* contained in the blood of infected animals to disappear in 15 minutes.

The blood of a guinea-pig which had been treated with emetic, on being inoculated a week afterward into another animal susceptible to the infection, does not communicate the disease; but as a general rule, three weeks after the administration of the emetic, recidivation is usually observed, which proves that in the webs of the tissues there still remain parasites not affected by the drug; so that to obtain lasting results, it is necessary to employ fractional sterilization, as is done in other protozoal diseases.

In consequence of these experimental results, we made some experiments on horses attacked with Derrengadera. In collaboration with Núñez Tovar we inoculated 5 horses and 2 mules which presented a great quantity of *Trypanosoma venezuelense* in the peripheral circulation. The dose used was from 1 to 1½ grams of emetic dissolved in 5.0 c.c. of sterilized water. The animals that were submitted to this treatment got markedly better, but in the end they showed signs of slight recidivation.

In 1920 a preparation under the name of "Bayer 205" — superior in efficacy to all the medicaments so far tried

in the different cases of Trypanosomiasis, both experimental and natural — was submitted to the consideration of the medical world. Hændel and Jœtten (1920) on the one hand, and Mayer and Zeiss on the other, pointed out almost at the same time that its chemo-therapeutical index for mice was 167. If we except the malady of Chagas, all experimental cases of Trypanosomiasis in small animals are cured in 12 hours. The cured animal remains a long time immune from infection, which is due to the fact that the medicament accumulates in its organism, so that the serum of animals treated may be used to cure others.

This action continues even when the serum has been heated to boiling point.

Mayer and Menk (1921) have been able to prove the presence of "Bayer 205" in the urine of man and of animals treated with that preparation.

When used as a prophylactic, "Bayer 205" renders mice immune from attack for many months.

In consequence of such flattering success, we procured from the manufacturers through the kind offices of Professors Fülleborn and Mayer of the Tropical Institute of Hamburg, a sufficient quantity of this medicament to begin experiments on a large scale. The following are the experimental results obtained:

Action in vitro.— Blood extracted by intracardiac puncture from a guinea-pig the 5th day following its inoculation with *Trypanosoma venezuelense*, was mixed in a solution of "205" at 2%. The microscopic examination made 2 hours afterward proved that the trypanosomes had not undergone the slightest alteration, either in their morphology or in their vitality.

Therapeutical effect. — Each of 10 guinea-pigs affected with Derrengadera was inoculated intraperitoneally with 0.03 of "205" on the 8th day following infection. They were examined daily for the period of 3 months, and 40 days following the experiment only 2 examples presented a few trypanosomes in their blood. The control animals all died during the 2nd and 3rd weeks.

Quantities of 0.075 to 0.10 of "Bayer 205" are toxic for the guinea-pig.

Permanent cure can be obtained in the domestic mouse with 0.003 of "205". With this dose the trypanosomes dis-

appear from the circulation after 24 hours. The infection of these animals by *Trypanosoma venezuelense* is prevented by doses of 0.003 to 0.004 for mice and 0.03 for guinea-pigs.

Brumpt (1922) succeeded in re-infecting 2 mice, cured of Derrengadera, with the same virus.

In consequence of these experimental results, and in obedience to a decree issued by the President of the Republic, General Gomez, the Public Health Department of Venezuela has been making preparations since the beginning of the present year to launch a campaign against this epizoötic.

Finally, we will show a film which represents the blood of a guinea-pig infected with *Trypanosoma venezuelense*, seen with dark-field illumination.

The photograph was taken at the rate of 16 exposures per second, which means $\frac{1}{32}$ of a second for each exposure projected on the screen.

The microscopic magnification used by us in this experiment was one of 760 diameters, but the views projected are considerably magnified; the red globules are seen as white-bordered disks and the trypanosomes are seen in the picture magnified 12,000 times their natural size.

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DISCUSSION

Dr. Herbert C. Clark (Opening the Discussion).— It has been very interesting to listen to Dr. Iturbe's paper on Derrengadera. My experience with this disease, or at least a disease quite similar if not the same, was gained in Panama where I had the opportunity to assist Dr. S. T. Darling in his study of "Murrina," which he reported at length during the years of 1910, 1911, 1912 and 1913. The terms "Murrina" and "Derrengadera" are considered synonymous in Panama. The disease in its natural transmission is confined to horses, mules, and donkeys. Our first contact with the disease was gained when it occurred among some horses and mules recently imported from the United States. These animals had been allowed to use the same pasture with native animals at Gatun.

Murrina has appeared in an epidemic form in the Canal Zone and immediate neighborhood in the Republic of Panama two or three times, the last time being in September, 1917. Cattle are not susceptible.

Darling, and later Lavaran, decided the pathogenic agent, *Trypanosoma hippicum*, had morphological and biological characters which differentiated it from other species of trypanosomes. In fact, Darling considered that the symptoms and the pathological features stamped Murrina or Derrengadera as a distinct disease and not to be confused with Naganna, surra, mal de caderas and Senegambian horse disease. I cannot recall a single case in which a horse or a mule survived the disease, although some lived for many months. I had one guinea-pig that lived almost a year after it was inoculated with the disease, but the usual length of life was 3 to 8 weeks. Dogs are easily infected, but I have never seen one naturally acquire the disease. During the fall of 1917 I placed several dogs among a herd of horses and mules that were naturally ill with the disease, yet none of the dogs ever developed it. A dog can pretty well protect itself against horse-flies, and this experiment was interesting from that standpoint. We have never been able to kill the trypanosomes in a sick animal without also killing the animal!

The nearest exception to this result was the intravenous use of tartar emetic during the epidemic of 1917. No trypanosomes were afterwards found in the blood of 20 animals treated in this manner, nor could guinea pigs be infected with the blood from these animals. Nevertheless all the 20 animals died in the course of a few months. The tri-oxide of antimony was given by deep intramuscular injections to 3 normal horses, which were then turned in with the sick animals, and these horses did not contract

the disease. Whether this is evidence of a protection given or a mere coincidence, I am not yet prepared to say.

This disease always claims a heavy toll among horses, mules and donkeys along the South Pacific coast of Panama and throughout the Canal Zone area. Animals can be in apparently good health for some days after the parasites can be demonstrated in the blood films. I was once called out to a ranch to see 3 sick horses, which were easily proved by microscopic examination to have trypanosomiasis. The owner was asked to bring out all other stock on his place (horses and mules). He had 20 head of these animals and there were three splendid ponies which he used to round up the other stock. I found trypanosomes in every one of these animals, and all showed the symptoms in due course of time. This is an important fact to keep in mind when one is called upon to establish a quarantine against the disease, because more than the visibly sick animals must be quarantined. It has been our method in the Canal Zone to make a blood survey on herds of animals and then quarantine or kill infected individuals. Screened stables were used for a quarantine post. The new treatment with "Bayer 205" was not known at the time we carried on our work.

I believe it has long been the opinion that some biting insect, presumably a tabanid fly (horse-fly) is the intermediate host of this disease. There are several kinds of horse-flies in Panama and my efforts to induce the disease by means of these have not met with success. Mechanical transmission, by other flies, harness, saddles, rubbing against stalls, etc., accounts for many infections. One can clip the ears of several guinea pigs and then place these animals in a pen with an infected pig that has had its ears freshly clipped and thereby infect the entire lot of them. I wish to congratulate Dr. Iturbe on his success in the experiments dealing with the fly transmission of the disease, and on his successful treatment of the disease with "Bayer 205," and to thank him for his very interesting report.

WHAT WE KNOW ABOUT HURRICANES

W. H. Pickering, S. B.

Tropical cyclones are known as hurricanes in the West Indies, as typhoons in the South Pacific, West Pacific, and China Sea, and as cyclones in the Indian Ocean. There are two classes of cyclones, tropical and extra-tropical, both marked by a low barometer and abundant rain. The hurricane resembles our northern cyclone, the wind rotating in the same direction. In tropical storms, however, the temperature is the same in all directions. The average annual frequency is 4 a year in some portions of the Caribbean; in Kingston we may not have the center of one more than once in every 10 years, but storms may pass near us and give us a severe blow. The China Sea has an average of 24 storms a year. Where the hurricane starts the diameter is about 50 miles, but it increases to 200, 500 and even to 900 miles. At the surface the winds blow in toward the center and then go upward and outward; at the center there is a nearly calm area.

Hurricanes usually start in the eastern Caribbean Sea and pass along the Atlantic coast, but are soon lost when land is reached. At the center the sky is clear, the winds light, blowing at from 10 to occasionally 30 miles per hour, but at a short distance from the center the winds have a velocity of perhaps 130 miles, rapidly decreasing at a distance of 200 miles again to 30 miles an hour. Before the hurricane, there are often 2 or 3 hot days, clear skies, and a slight rise in the barometer. Along the eastern horizon will then be seen light feathery clouds. That means the center of the storm is from 100 to 200 miles distant. The barometer then begins to drop, the breeze is still gentle, and the air sultry. At sunset the western sky becomes lurid, the clouds thicken and obscure the sun, the wind increases to a gale, and rain begins to fall. That means the hurricane is 50 miles away. Then the barometer lowers rapidly, the wind moans, then roars, the thunder peals, and the rain comes in horizontal sheets.

If, as the wind slowly shifts in direction, it gradually dies down, that means that the hurricane has passed, but if the

wind suddenly falls to a light breeze or a dead calm and the sky clears, that is the danger signal to the sailor, who knows he is then in the "eye of the storm." Suddenly the wind rises again, but now from the opposite direction, causing terrific cross seas; the wind and rain are as severe as before, then after a few hours they die down, the sun comes out, and all is fine once more. The whole storm may last 24 hours, but as Jamaica experienced in 1912, it may last 3 days, with constant high winds blowing at from 50 to 60 miles and with sheets of rain. At sea, a long rolling swell precedes the storm 3 or 4 days, and thus gives the first notice of it. Mariners always avoid running before the wind, but keep the wind on the starboard beam if north of the Equator. In the West Indies all storms come from the east. Storms passing to the south are more severe than those going to the north of us.

As to the explanation of why hurricanes occur, the so-called doldrums stretch along the Equator, and move north and south with the sun. In the doldrums the weather is moist, hot and cloudy, with light winds, frequent calms and showers. The doldrum region is the motor that runs the whole atmospheric circulation of the globe. We are in the habit of thinking that all air currents or winds are horizontal, but it is not so. On a calm sea there are areas marked with little ripples and others that are smooth. The smooth areas show where the air is rising from the water, and the ripples where other currents are descending. The air near the surface is hot and the upper air cool. The hot air tends to rise. Little clouds floating over the sea show the hot areas. If the clouds are larger there comes a shower; if still larger, a small storm, and if very large the air, instead of simply rising, is drawn in toward the center in great spirals. In rising, the moist air gives out heat, and that rising current increases the draught. The more air, the bigger the draught, and the worse it gets, because the moisture is carried up from the sea, and the trouble then begins.

In the West Indies the doldrums are farthest north in August and September, which are the months when hurricanes most frequently occur, but hurricanes have been experienced here in June and in November. The Atlantic Ocean is the only sea where the doldrums never go far south of the Equator, and the South Atlantic is the only ocean that never has a hurricane.

ACTIVITIES OF THE MEDICAL DEPARTMENT OF THE UNITED FRUIT COMPANY

W. E. Deeks, M. D.

I have been asked to tell the story of the development of the United Fruit Company—particularly of its Medical Department—and to give an account of its present organization and activities.

The Company was incorporated in March 1899, at which time commercial enterprise in those countries bordering the Caribbean Sea was greatly handicapped by the unhealthy and insanitary conditions existing there, and the prevalence of endemic and epidemic diseases. The record of industrial progress in the Tropics is really the record of medical and sanitary progress, for agricultural development and commercial activity on a large scale are impossible until medical science brings tropical disease under control, and sanitation transforms pestilential areas into healthy localities.

From the very beginning the United Fruit Company realized the necessity of combating insanitary conditions in the Tropics. A Medical Department was therefore created. For over a quarter of a century it has carried forward a relentless war against disease. The commercial success of the Company is largely due to its accomplishments in reducing the prevalence of those diseases formerly responsible for an appalling morbidity and mortality rate. Yellow fever and smallpox as serious menaces have been eliminated, and the incidence of other fatal or debilitating diseases has been greatly reduced. While Malaria and Hookworm are still problems of considerable importance, progress is being made from year to year, and the localities where the Company operates now show health records which compare favorably with those of communities in the temperate zone.

Some idea of the extent and scope of the activities of the Medical Department may be conceived when we realize that the plantations of the United Fruit Company cover about 2,000,000 acres of land (of which approximately one-

half is cultivated), located in Colombia, Costa Rica, Cuba, Guatemala, Honduras, Jamaica and Panama.[1]

The Central American and Colombian divisions are directly concerned in the production of fruit — chiefly bananas[2], and the Cuban divisions in the production of sugar.[3]

It is economically impracticable to sanitate all the areas contained in the Company's plantations[4], but strenuous efforts are made to keep all lands in the vicinity of dwellings in a sanitary condition, and mosquito-breeding places which cannot be eliminated by filling or draining are larvacided regularly.

The Company employs approximately 67,000 persons, and has created an extensive system of hospitals and dispensaries for the benefit of these employes and their dependents, as well as for other inhabitants in or adjacent to the plantations. It is estimated that 150,000 persons are dependent upon the Medical Department for medical and surgical service, and a still larger number enjoy benefits from its sanitary and preventive work. At the present time it operates eight large, modern hospitals, handling approximately 28,000 cases a year, while the dispensaries, located at convenient points on the plantations, treat approximately 230,000 patients yearly. Non-employes of the Company comprise about 15% of these patients.

Hospitals in the Tropics call for special arrangements and details to insure comfort and efficiency. Nearly all of the Company's hospitals are of steel and concrete and are built in accordance with a standard plan, which has been devel-

[1] This area may be appreciated when we consider that the Company owns or leases approximately 3,000 square miles of territory, whereas the State of Rhode Island contains only 1,248 square miles, Delaware 2,390 square miles, and the Panama Canal Zone less than 500 square miles. The Company operates 1,450 miles of railways, 675 miles of tramways, and over 3,500 miles of telephone and telegraph lines.

[2] During the past ten years the Company has shipped from the tropics 293,000,000 bunches of bananas. It also produces a large quantity of cacao, coconuts, citrus fruits and other tropical foodstuffs.

[3] Two large modern sugar mills are located in Banes and Preston respectively, each having a daily average capacity for grinding 7,000 tons of cane. They represent a combined maximum annual output of 1,400,000 bags (200,000 tons) of raw sugar. Adjacent to one sugar mill is a distillery, converting the final molasses into alcohol-ether motor fuel, used instead of gasoline in internal-combustion engines.

[4] On the plantations there are approximately 43,000 head of livestock.

oped as the result of study and experience. This plan is available for other agencies operating under tropical conditions. The hospitals are located so as to best serve the needs of each plantation. Every hospital is modern and completely equipped with all facilities for the diagnosis and treatment of diseases and the care of patients, including an up-to-date surgical and X-ray equipment, laboratory, outpatient department and steam laundry. Medical and nursing staffs are comfortably housed in separate buildings with pleasant surroundings.

In the centres of population and about individual dwellings, modern sanitary conveniences have been installed; the quarters of employes are modern and are under constant supervision of the Medical Department, which also directs the sanitary measures on the plantations. The lack of education of the laboring classes makes the problem of reducing infectious diseases a difficult one, but gradual progress is evident, despite the migratory habits of the laborers.

The welfare work of the Company in the Tropics has assumed large proportions and has a direct bearing on the health and contentment of the employes. The Company has built and maintains churches and schools to meet denominational and racial requirements, and has erected and equipped club houses and amusement halls to provide entertainment for employes. It has also provided baseball grounds, and tennis courts, and in some plantations, where practicable, golf grounds and swimming pools. It operates extensive merchandise departments for the convenience of the local communities, and has also installed and maintains hotels, laundries, ice plants, bakeries, electric-light plants, water-works, and sewerage systems, transforming the zone of its tropical operations into modern, sanitary and healthful areas. In some places the Company has built ports including docks and warehouses to facilitate its operations.

The annual expenditures of the Medical Department amount to approximately $1,000,000. In addition the Company spends yearly $200,000 for sanitation; and an additional sum of $300,000 for street cleaning and the maintenance of parks, which is directly related to sanitation. It has $3,000,000 invested in water supply and electric light plants.

The Company has established powerful Radio Stations at

various points in the Tropics and in the United States. The Medical Department, utilizing these facilities, maintains a free Radio-Medical Consulting Service, so merchant ships can secure medical advice from the Company's hospitals, or from its steamships carrying physicians.

While the principal activities of the Medical Department naturally relate to the care of employes in the Tropics, its activities in the United States are sufficiently important to warrant some comment.

At Boston,[1] New York and New Orleans, the Medical Department renders dispensary service to employes. All prospective salaried employes in both domestic and tropical divisions are given a thorough physical examination — the greater proportion under the supervision of the Medical Department. This Department also examines all steamship crews before each voyage begins and has supervision of the sanitation of the steamships, as well as of all questions pertaining to quarantine and immigration matters affecting the Company's interests.

All vessels are thoroughly rat-proofed and maintained in a sanitary condition under the direct supervision of the Medical Department[2]. Doctors are employed aboard passenger steamships, and the result of proper vigilance on their part is shown by the comparative absence of contagious diseases, despite the volume of traffic handled[3].

It will be seen from the above summary that the work of the Medical Department is both varied and extensive. It offers unusual opportunities for the study of tropical prob-

[1] At the port of Boston the medical staff also renders service to the employes of the Revere Sugar Refinery, a subsidiary company situated in the Charlestown district of Boston. A fleet of steamships of the United Fruit Company transports the raw sugar directly from the plantations to this refinery, which has a daily refined-sugar output of 4,000 barrels. The refinery also operates a modern fireproof cooperage plant with a daily output of 5,000 barrels and 4,500 wooden cases.

[2] The Company operates a fleet of approximately 80 steamships, including its chartered vessels and those of its subsidiary, Elders & Fyffes, Ltd. All the steamers owned by the Company are oil-burners, specially built and designed for tropical service, and equipped with radio. These steamers furnish regular passenger, mail, and freight service between the Atlantic ports in the United States and Cuba, Jamaica, Central American countries and Colombia; and through the connecting lines at the Panama Canal, with the west coast of South America. In conjunction with the passenger traffic, the Company maintains two of the most modern hotels in the Tropics, the Myrtle Bank Hotel at Kingston and the Hotel Titchfield at Port Antonio.

[3] The fleet has carried 500,000 passengers and moved 15,000,000 tons of freight during the past ten years.

lems and the investigation of rare diseases and exotic infections. Scientific workers are welcome. It is the aim and policy of the Medical Department to become increasingly efficient—particularly along scientific lines and it was this desire which prompted the holding of the present Medical Conference, which should prove a great stimulus to us as well as to others interested in preventive medicine throughout the Tropics.

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